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GENETIC AND CONSTITUTIONAL ASPECTS OF DIABETES MELLITUS

BY

SVEN E. NILSSON

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SVEN E. NILSSON

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HÅKAN OHLSSONS BOKTRYCKERI



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ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 375

FROM THE DEPARTMENT OF MEDICINE, KRISTIANSTAD CENTRAL HOSPITAL, KRISTIANSTAD
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AND

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ASPECTS OF
DIABETES MELLITUS

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SVEN E. NILSSON

LUND 1962

Translated by L. James Brown

Printed in Sweden

L U N D

HÅKAN OHLSSONS BOKTRYCKERI

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I. INTRODUCTION

The purpose of the present investigation was to elucidate and evaluate:

1. *The hereditary background of diabetes, especially of the juvenile type.*
2. *Constitutional features associated with an assumed diabetes gene.*
3. *Constitutional and environmental factors favouring the manifestation of diabetes.*
4. *The effect of manifest diabetes on physical development and intellectual endowments.*
5. *The results of intravenous glucose tolerance test in various groups with different risks of being carriers of an assumed diabetes gene.*

The investigation was carried out chiefly on 3 groups of young males:

with manifest diabetes;
non-diabetic but, owing to diabetes among their relatives, apt to be carriers of a diabetes gene, and
non-diabetic, without any known heredity for diabetes.

Differences in persons with manifest diabetes compared with non-diabetic relatives of diabetics were ascribed to:

factors favouring manifestation and thought to be observable particularly during perimorbid development, changes due to the disease.

Differences found on comparing healthy relatives of diabetics and of non-diabetics were ascribed to:

factors associated directly with an assumed diabetes gene,
inherited factors increasing manifestation among the relatives of the diabetic.

*

Since all males in Sweden are liable to national service a group of military conscripts of uniform age and registered on the same occasion provided a suitable material for the investigation. On induction all members of an annual class and residing in one and the same military registration district were therefore given a written inquiry as to whether they or any of their relatives had or had had diabetes.

An advantage of such a group is that it is representative of a definite geographical region and is not biased by various non-geographical selection factors, always difficult to evaluate. Since the subjects were of uniform age, possible sources of error involved by age-differences were avoided. On the other hand, this uniformity of age meant a limitation of the universality of the material. This limitation could, however, be overcome to some extent by collecting data on the earlier development of the probands and the state of their relatives, the latter being specially valuable for the investigation when diabetics.

The weights and heights of the probands at birth and during school age were obtained partly from the records at departments of obstetrics and from the records kept by school-nurses.

The 18-year-old probands proved to possess but meagre knowledge of various familial details of relevance. In contrast, the middle-aged mothers of these probands, all of whom received written inquiries, gave extensive information on illnesses the members of the family had had, on the birthweights of their children, on their own weights and on the weights of their husbands, etc.

A decisive advantage of a series consisting of conscripts is also the ready availability of age-matched controls.

After collection of this group of 18-year-old conscripts in whom manifest diabetes might be expected, on genetic grounds, to develop more often than in the population in general, a glucose tolerance test was done on about half of the probands and their controls, to ascertain any correlation between the risk of manifest diabetes, as judged from the results of glucose tolerance tests and from genetic calculations.

*

Since the penetrance at 18–19 years of age is low, the group of diabetics was extended to include diabetics in 2 military registration districts and born in the years 1934–1942. This implies a difference between the groups, which was, however, counteracted by the use of data noted in the military record sheets of the diabetics at the time of induction and by treating the probands from the two military registration districts separately.

*

As the material lent itself well to an all-round examination, numerous data considered useful in the elucidation of somatic, mental and hereditary aspects were collected and, when possible, arranged in such classes as to fit a Gaussian curve. Correlations between all factors studied were then calculated with an electronic data machine.* Diabetics and non-diabetics were treated separately.

The correlation coefficients found for the diabetics and for the non-diabetics were compared, and those coefficients considered of relevance were analysed further.

The description of the results includes chiefly those coefficients and other values bearing directly on the problems outlined above. Some supplementary coefficient-tables demonstrating various methodological problems will also be given in Appendix III.

Any attempt to give a detailed survey of the voluminous literature on the aspects pertinent to the present investigation would be futile. It was therefore decided to limit references to a reasonable minimum and to draw generously on recent monographs by DANOWSKI (1957), JOSLIN *et al.* (1959) and WILLIAMS *et al.* (1960).

A brief survey of previous relevant investigations is given in the respective chapters.

* I thank fil. kand. Torgil Ekman for kind help with the treatment of the data in the electronic data machine.

II. MATERIAL

The material comprised 2 series of young males:

Series A — young diabetic males

Series B

Br — young male relatives of diabetics

Bc — controls

SERIES A

119 males with manifest diabetes mellitus, born in the years 1934–1942 and representing about 90 % of all diabetics in this age-group, who at the time of the investigation were living in Scania, the southernmost province of Sweden with 869,983 inhabitants on Jan. 1, 1958. Scania is divided into two administrative areas, namely Kristianstads län with 258,046 inhabitants (1958) occupying the north-eastern part, and Malmöhus län with 611,937 inhabitants (1958) occupying the south-western part of the district and containing Malmö (217,330 inhabitants), the largest town in Scania. The social structure is elucidated to some extent by the fact that the urban population in Kristianstads län represents 22 % of its total population, as against 67 % in Malmöhus län, or 48 % if Malmö be excluded (*Statistisk Årsbok för Sverige*, 1958).

The province of Scania has, in addition to 2 university hospitals at Lund and Malmö, 6 other hospitals with special departments of internal medicine. In view of the organization of the medical service in this district, it was assumed that most

diabetics of the ages in question were on the registers of the above-mentioned hospitals, or of a few other physicians particularly interested in the disease. These registers were therefore searched for male diabetics born in the years 1934–1942. The number found was then compared with the number of diabetics in the military registers, where notes are made of subjects suffering from diabetes, exempting them from military service.

The differences between the military registers and the hospital records, which are apparent from Table 1, are due in part to removal of probands during the interval between registration, when the probands were 18–19 years of age and when exemption was usually granted, and the collection of data for series A (July 1959–Feb. 1960).

It is clear, however, from Table 2 that no difference in weight, height or result of intelligence test was found between members of series A and those diabetics noted in the military registers but not belonging to series A, which could consequently be considered representative of the age-class investigated.

Certain data on persons immediately following the members of series A in the military and school registers were selected for comparison with equivalent data on the probands.

SERIES B

18-year-old males belonging to the 6th military registration district, and registered

Table 1. Composition of Series A.

	Belonging to:		Total
	6th mil. reg. distr.	7th mil. reg. distr.	
Personally examined	60	49	109
Not personally examined	7	3	10
Total	67	52	119
Noted as diabetic in military register	71	68	139
Noted in military register but not in series A	15	20	35
In series A but not in military register	11	4	15

Table 2. Data from military registration sheets on diabetics born 1934—1941 belonging and not belonging to series A.

	n	Weight at induction (mean)	Height at induction (mean)	Mean score intell. test (mean)
Series A	93	63.2 kg. SD 8.2	173.8 cm. SD 7.3	5.24 SD 1.95
Noted as diabetic in military register, not belonging to series A	35	61.2 kg.	173.2 cm.	5.24

in the autumn of 1959. The 6th military registration district consists of the northern part of Scania, its southern boundary dividing the province into 2 parts, each containing about half of the population.

According to Swedish law, every male is obliged to present himself for induction in the year he becomes 18 years of age and to do his military service the following year.

Under special circumstances, a man may appear for induction somewhat earlier or later. Of those who were registered relatively early or late, however, only those were included in the present investigation who were registered the year before or the year after they filled 18 years, which was 0.5 % of the whole series B.

Personal appearance is obligatory for all

men called up, unless they can produce a medical certificate that they are suffering from some disease rendering them incapable of doing their national service. Therefore 20 (0.7 %) of the men in the year class did not present themselves. These consisted of persons with mental disorders, epilepsy, severe orthopaedic diseases, or with poor vision, etc.

Diabetes is regarded as a ground for exemption from military service, although most diabetics present themselves for examination.

*

Series B was divided into two subseries, Br and Bc.

Series Br consisted of conscripts with diabetic near relatives, *i. e.* sibs, parents,

Table 3. Composition of series B.

Number of men liable to registration in the 6th military registration district 1959	2,834
Registered elsewhere	155
Exempted on medical grounds and not presenting themselves for registration	20
Total	2,659
Br:	
Diabetes in family reported on registration	243
Erroneous report on heredity — excluded	11
Erroneous report discovered by answers given by mothers — transferred to Bc	4 228
Persons originally assigned to Bc but, after report of diabetes heredity from mothers, transferred to Br	9
Total Br	237
Bc:	
Recruits with Army number immediately after those of the Br probands	243
Transferred to Br — cf. above	9 234
Transferred from Br to Bc — cf. above.	4
Total Bc	238
Minus unexamined seamen	8
Number of diabetics in year class	6

sibs of parents, grandparents and 1st cousins. As controls of series Br use was made of conscripts registered immediately after the Br probands. The control series was called Bc.

The composition of series B is given in Table 3.

In May-June, 1960, 209 subjects out of 475 registered in B were examined by the author at their barracks, where supplementary data were obtained and glucose tolerance tests were performed.

The following groups were not included in that personal examination:

- I. (154 persons). Conscripts whose national service was postponed until 1961 because of special circumstances, *i.e.* recent lowering of the age for national service and unusually large number of men being liable to service that year.
- II. (44 persons). Conscripts called up later in 1960, *i.e.* those belonging to the navy and the coast artillery, as well as some others with special training.
- III. (32 persons). Conscripts of units stationed far away from the investigation laboratory (generally more than 250 kilometres).
- IV. (18 persons). Exempted by disease at military registration. Mostly persons with orthopaedic diseases or poor vision.
- V. (10 persons). Conscripts who had been enlisted but who could not be examined owing to some accidental disease, etc.
- VI. 8 persons belonging to series Bc who did not appear for induction, all of them were seamen.

In an attempt to form a rough opinion of the effect of these exceptions on the results, the mean weights and heights of these groups were calculated and compared with the values for the whole series and the group personally examined by the author(See Appendix I, Table 1).

Groups IV and V seem to differ to some extent, but since these groups were small, any influence they might have exerted was considered negligible.

*

Certain differences may be suspected between series Br and Bc in addition to diabetic relationship. Assignment to series Br requires a certain knowledge of relatives so that persons belonging to groups with better knowledge of their relatives may be over-represented in this series. This bias will, however, be negligible concerning those probands assigned to series Br because of diabetes in their brothers, sisters or parents.

In order to check whether differences in composition between series Br and Bc were due chiefly to a preponderance of diabetes in certain sociologic groups or to differences in knowledge of relatives, the probands in series Br and Bc were classified according to occupation. Those probands in Br with diabetic parents or sibs were taken together as a separate group. The distributions are given in Appendix I, Table 2, which shows that series Br contained a relatively high percentage of students, while Bc contained a relatively high percentage of industrial workers. The distribution of probands with diabetes in close

relatives did not differ appreciably from that in the entire Br series, which suggests that the differences found between Br and Bc were due to an over-representation of diabetes in certain sociologic groups rather than to differences in knowledge of relatives.

It is also clear from Appendix I, Table 2, that the distribution according to occupation of those examined by the author personally was somewhat different from that of those who were not examined personally. Thus, the latter group contained a larger percentage of students who had been granted postponement of their national service on educational grounds.

In order to obtain a measure of the relation between a given occupation and physical development, the mean weights and heights of the men at the time of induction were also calculated. This made it possible to correct these values in series Br to match the composition of series Bc.

Since series B is fully comparable with only those probands of series A who belonged to the 6th military registration district, it was considered desirable to compare the sociologic composition of series A and B after division of series A according to the military districts to which the probands belonged. The probands were then grouped according to the occupations of the fathers since the probands' occupations in series A and B were not fully comparable owing to differences in age levels. The results of the comparisons are summarized in Appendix I, Table 3, which shows that the differences found were not significant and could be ignored on appraisalment of data influenced by sociologic factors.

III. METHODS

PHYSICAL EXAMINATION

Collection of data on weight and height

At birth

At 13 years of age

At about 18 years of age

Body composition

Skeleton

Muscles

Fat tissue

Blood pressure

Pulse rate

COLLECTION OF DATA ON WEIGHT AND HEIGHT

At birth. Of all children born in 1941 in Kristianstads län, in Malmöhus län and in the town of Malmö, 72 %, 90 % and 96 % (*Sveriges Officiella Statistik 1941*), respectively were born in hospitals, where weights and lengths of the newborns were regularly noted. The weights and lengths of the probands were therefore collected as far as possible from the hospital records. However, since many of the probands were not born in Scania and since some could not be traced in the hospital records, information was obtained in this way on only 53 % of the probands in series B and 41 % in series A.

In addition, information on the weights of the probands and their sibs was obtained from their mothers. These data agreed surprisingly well with those collected from the hospital records, the mean weight and range being just the same. As

to the 167 probands of series A and B whose birthweights were obtained from the mothers as well as from the registers of the obstetric departments, the same mean value of 3.56 kg. was found for both groups. In 54 cases the weights reported were the same as those noted in the hospital records; in 55 the difference was at most 100 g.; in 28 the reported weights were more than 100 g. higher; and in 30, more than 100 g. lower, than those noted in the records.

Information on the birthweights of the probands was thus supplemented and then covered 79 % in series B and 75 % in series A. Information was obtained of the birthweights of the sibs of 49 % of the probands in series B and of 47 % in series A.

For special purposes (see Chapter VI) information was also collected on the weights and lengths of all children born at the departments of obstetrics in Kristianstad in 1941 and in Malmö 1960.

*

At 13 years of age. At the time of the investigation school attendance was obligatory until the age of 13 years. In order to collect as large a series of children with diabetes as possible, this age was chosen for the investigation. Data on 13-year-old boys were collected by written inquiries to school-nurses of the districts in which the probands had attended school.

The data were obtained from the records of the routine annual medical examination by a school-doctor or a school-

nurse. As a rule, the measurements had been taken with the children stripped. Measurements were not obtainable from all of the probands because some of them had not been examined at 13 years and because some of the school-records were not complete. For those born in 1934–1937 no values at all were obtainable because the records had been destroyed. Data were obtained on all together 114 subjects of series B out of 209 examined personally by the author, *i. e.* 55 %. In series A the corresponding numbers were 48 out of 119, *i. e.* 40 %.

*

At induction. The weights, heights, and circumferences of the chest noted on medical examination at induction were obtained from the military registration cards. All measurements were made with the subjects naked, and by trained personnel.

The heights and weights were also measured by the author on the occasion when other somatic measurements were made. Shoe sizes were then also noted.

*

Weights were given in kilograms with one decimal, with the exception of newborns, whose weights in the hospital records were generally given with two decimals.

Heights were given in centimetres.

BODY COMPOSITION

The skeleton, muscles and fat tissue are responsible for the major part of total body weight, and show the widest range of variation.

Judging from the few anatomical dissections on record (For survey see VON DÖBELN, 1956) and data on the proportion of fat at different ages as measured densitometrically (BROZEK *et al.*, 1953,

LIM & LUFT, 1961) the mean ratios between the volumes of fat tissue, skeleton and muscle tissue in a normal 20-year old male is roughly 1: 2 : 4. These ratios differ with dietary habits and physical exertion, but genetic disposition is probably of great importance.

*

Detailed analyses of the effect of different hormones on growth have been performed mainly on animals and are therefore not strictly applicable to human beings. It is evident that the hormones participating in the regulation of growth do not affect all parts of the body to an equal degree, and that the growth response of a given tissue varies with the pattern of the stimulus (RUSSEL & WILHELMI, 1958, SCOW, 1959).

*

Various methods are available for assessment of the relative amounts of the above-mentioned types of tissue, but only those that could be used in a field investigation could be considered.

In the choice of methods due attention was given to the work of LINDEGÅRD (1953, 1956), which was also partly performed on conscripts and allows of a comparison of values and correlations found in the present investigation. The terms length factor, sturdiness factor, muscle factor and fat factor in the sense used by LINDEGÅRD were utilized for differential somatologic classification.

*

Skeleton. The skeletal framework is described by a length factor reflecting endochondral growth, and a sturdiness factor reflecting appositional growth.

The *length factor* can be assessed by different measurements.

In addition to the body height, in the

present investigation the length of the tibia and of the radius on the right side were measured. These measurements were made according to MARTIN (1928) and LINDEGÅRD (1953, 1956). The body-height was thought to represent mainly the length factor even if influenced by the sturdiness factor and possibly by exogenic factors — *e.g.* type of work and physical training during adolescence, etc.

The growth curves for the shaft bones and the truncal height are not always parallel (STOLZ & STOLZ 1951). It is known that in the prepuberal years the legs grow faster than other parts of the body. In males the legs are longer than in females because of later puberty and later closure of the epiphysis. When testosterone secretion has started it seems to initiate truncal height growth resulting in a higher sitting height of males. (For survey see TANNER, 1955).

The *sturdiness factor* of the skeleton was expressed by the right femoral condylar breadth and the right bistyloid radio-ulnar breadth measured according to MARTIN (1928) and LINDEGÅRD (1953, 1956).

The factors determining condylar breadth are probably largely the same as those dictating the cross sectional area of the muscles, and muscle strength. It is possible that the breadth of the other parts of shaft bones are dependent mainly on the volume of the marrow space, which seems to vary in a different way (TANNER *et al.*, 1959). Some correlation-coefficients of length- and sturdiness-factor are given in Appendix III, Table 3 and 4, respectively.

*

Muscles. As mentioned above, cross-sectional areas of the muscles seem to vary with the sturdiness of the skeletal framework (LINDEGÅRD, 1953, 1956). The volume of the muscles may also be influenced by a length-factor closely correlated with the length-factor of the skeleton.

In addition some special methods have been described for estimating muscularity. The most valuable of these appears to be measuring muscle strength with a dynamometer (STOLZ & STOLZ, 1951), the recording being considered proportional to the total cross sectional area of all fibers of a given muscle (LINDEGÅRD, 1953).

In the present investigation the strength of the handgrip and the thrusting and pulling power of the shoulder muscles were measured according to STOLZ & STOLZ (1951). All of the dynamometric recordings were made 3 times, and the best performance was noted.

The men were requested to press the dynamometer gradually, *i.e.* not by jerks. During the measurements the persons were in the erect position with neither the arms nor the hands touching the trunk. The tests were performed at intervals of at least 3 minutes. The dynamometers used were tested against known weights on 3 occasions during the investigation.

STOLZ & STOLZ (1951) found a discrepancy between the dynamometric results and other events of adolescence in a longitudinal study: in their material there appeared to be a peak of strength increase in boys about 1½ years after the peak of height growth and 1 year after the peak of weight growth. It seems probable that the growth of muscle volume at this age level coincides chiefly with the increase of body weight.

The difference between growth spurt and strength spurt may be ascribed to the continuous increase of androgen secretion during the years following the period of maximal growth (TALBOT *et al.* 1943). The increase in the volume of the muscles may be due mainly to an increased activity of growth factors, *e.g.* the pituitary growth hormone, while the increasing strength may represent "the effect of adrenocortical and testicular hormones on the protein

structure and the enzyme systems of the fibers" (TANNER, 1955).

The shoulder muscles, on which most interest was focused in the present investigation, seem to be particularly sensitive to testosterone (RUSSEL & WILHELM, 1958).

LINDEGÅRD (1956) recognizes mainly two factors deciding muscularity, *i. e.* an environmental-stable factor closely related to the skeletal sturdiness factor, and a labile factor dependent on training. The range of the latter is believed to vary from muscle to muscle. The strength of the handgrip has been shown to be rather independent of muscular training and is believed to be less influenced by the labile factor. Some correlation coefficients of the muscle factor are given in Appendix III, Table 5.

*

Fat tissue. The amount of fat tissue was assessed by two methods.

The *first* method consisted of measurement of skin fold thickness by calipers for assessing the amount of subcutaneous fat tissue (SKERLJ, BROZEK & HUNT, 1953). The values obtained by this method are influenced by epidermal thickness and a somewhat varying proportion between fat tissue and connective tissue of the subcutis. Epidermal thickness may be regarded as representing 2–3 mm. of the skin fold at the sites measured (EDWARDS, 1950).

The sites at which the measurements were made in the present investigation were: *back* just caudal to the scapula, *lateral part of thorax* over the lower ribs, midway between the axilla and the iliac crest, and on the *abdomen* in the right midclavicular line at umbilical level. These measurements have been found to be closely correlated with the total amount of

subcutaneous fat tissue (LINDEGÅRD, 1956, PASCALE *et al.*, 1956).

The *second* method was based upon estimation of fat tissue, as judged by the difference between the fat-free weight and total bodyweight. Various methods have been used to assess the fat-free weight. VON DÖBELN (1959) introduced a method based upon a regression calculation of values from measurements of various skeletal dimensions using the formula $FFW = 15.1 (H^2 \cdot F \cdot R)^{0.712}$ where FFW is fat-free weight, H the height in metres, F total femoral condylar breadth (left + right) and R total bistyloid radio-ulnar breadth (left + right) in centimetres.

The distribution and the amount of fat tissue is dependent not only on dietary habits, but also on endocrine factors. Before puberty the distribution of the fat is roughly the same for both sexes, while later the amount of fat appears to increase more in females (BROZEK *et al.*, 1953). As to the distribution in males, the fat tends to accumulate on the trunk, and, regarding actual age levels, particularly on its posterolateral aspect (EDWARDS, 1951).

According to BJURULF (1959), the fat factor is determined by two components, *i. e.* one constitutional, stable component represented by the number of fat cells and one labile, dependent on environments represented by fat cell size. The former seems to be correlated with hair growth, especially on the chest. Some correlation coefficients of the fat factor are given in Appendix III, Table 6.

BLOOD-PRESSURE

Blood-pressure was measured with a mercury Erkamanometer, after the subject had been resting on the examination table for at least 3 minutes. The diastolic pressure was registered as the pressure at which the sounds began to fall away

abruptly. The values were recorded in 5 mm. Hg steps. Some correlation coefficients of blood-pressure are given in Appendix III, Table 7.

PULSE RATE

The pulse rate was measured during 30 seconds immediately before and 30 seconds immediately after the injection of glucose, and the mean of the two determinations was calculated.

*

The most important correlations between different somatic tendencies are given in Appendix III, Table 1, which gives the following correlations in a normal male population and relevant to the later discussion.

1. Body weight at 19 years of age is equally dependent on length, sturdiness, muscle and fat factors.

2. Body height at 19 years of age is not correlated with the fat factor.

3. Weight and height at 19 years are closely correlated with weight and height at 13 years.

4. Birthweight is correlated with fat-free weight at 19 years, but not with the fat-factor.

5. Birthweight of child is correlated with the weight and height of the mother at 50 years but not with the weight or height of the father at this age.

6. The fat factor of the male at 19 years is correlated with the weight of the mother at 50 years, while his height and fat-free weight are likewise correlated with the mother's height but not with her weight.

7. The height and fat-free weight but not the fat factor of the male at 19 years of age are correlated with the father's weight and height at about 50 years.

8. The parents' heights, but not their weights, are correlated with one another at 50 years.

INTELLIGENCE TESTS

The intellectual endowments were assessed from the points scored by the probands in the intelligence test performed at induction. This test is based partly on the American "Army general classification test" (BITTNER, 1947) and modified in connection with the general intelligence testing of Swedish conscripts performed since 1944, and described by HUSÉN & HENRICSON (1951). The test has gradually been altered, so that the results from different years are not strictly comparable.

The test consists of sub-tests bearing on various aspects of intelligence. Thus, in 1959 the following types of subtests were used.

- A. Questions illustrating capacity to understand instructions.
- B. Vocabulary tests — *i. e.* differentiation of words with different meanings.
- C. Spatial tests — assembly tests.
- D. Questions illustrating ability of technical comprehension.

The results of the sub-tests are combined in a mean score. To describe the subtests as well as the mean score, a 9-grade scale of a special form is used, the distribution of which is demonstrated in Table 4. Correlations between different subtests and between subtests and the mean score are given in Table 5. In Table 6 means of mean scores from different years are demonstrated, from which it is evident that the results of the test in 1959 were noticeably low, chiefly owing to a low mean point of sub-test A (Table 4).

*

The connection between intellectual level and somatic development, family structure and other sociologic conditions is demonstrated in Appendix III, Table 2. These figures coincide with the comparable

Table 4. Distribution of 465 persons in series B according to results of subtests and mean score of intelligence testing in 1959.

test \ score	1	2	3	4	5	6	7	8	9
Subtest A	42	61	77	92	89	65	22	11	6
B	22	31	70	127	88	80	28	16	3
C	25	39	49	93	83	94	49	21	11
D	20	56	67	92	93	81	39	14	3
mean score	10	71	54	85	121	66	35	18	5

Table 5. Correlation coefficients between subtests, and subtests and mean score of intelligence tests.

	A	B	C	D	mean score
Subtest A		0.69	0.51	0.57	0.82
B	0.69		0.51	0.59	0.82
C	0.51	0.51		0.56	0.78
D	0.57	0.59	0.56		0.81
mean score	0.82	0.82	0.78	0.81	

n=465

For evaluation of significance, see Appendix V.

figures of HUSÉN (1951). Thus, there seems to be a correlation between test results and height, youths with higher intelligence being tall for age. This was however, not accompanied by any increase of the length factor expressed as tibial or radial length.

No correlations were found with certainty between the test results and other somatic radicals, except for a readily understandable negative correlation between intelligence and bistyloid breadth, the latter being increased in those who had been doing heavy work.

A small number of children, especially in the families of the proband and his mother, seemed to be associated with a higher intelligence level.

SOCIOLOGIC DESCRIPTION

The work and the social environments of the probands were described on the basis of the following factors with classes that could be graded in relation to one another.

- I. *Nature of the work* was assessed by rough estimation of the demands placed on the physique and intelligence of the proband. In each group 3 classes were recognized according to the following principles:

- a. *Physical requirements* of previous occupation

1. Little muscular exertion. Most

Table 6. Mean scores of intelligence testing achieved in different years.

Born	Years of test	Series	n	mean $\pm$ SE	Mean of all tested 6th and 7th mil. reg. distr. ¹
1934	1953	A ²	22	4.8 $\pm$ 0.3	
1935	1954	A	14	5.6 $\pm$ 0.4	5.0
1936	1954 ³	A	30	5.7 $\pm$ 0.3	5.1
1937	1955	A	20	5.4 $\pm$ 0.3	5.3
1938	1956	A	30	5.2 $\pm$ 0.3	5.2
1939	1957	A	28	5.1 $\pm$ 0.3	4.9
1940	1958	A	28	4.9 $\pm$ 0.3	5.3
1941	1959	A	20	4.5 $\pm$ 0.3	
1941	1959	B	465	4.5 $\pm$ 0.1	

¹ according to: Instruktion för provledare, 15. uppl. Militärpsykologiska institutet, Lund 1959.

² in this table A means diabetics + their matched controls.

³ in 1954 induction-age was lowered from 19 to 18 years.

office clerks and youths attending school belong to this group.

2. Moderate muscular exertion, *e. g.* shop assistants, workers in light industry, etc.

3. Considerable muscular exertion, *e. g.* farm labourers and workers in heavy industry, etc.

b. *Mental requirements* of previous occupation

1. Employees in occupations requiring little mental work.

2. Relatively independent work (this includes middle school and the first years of secondary school).

3. Intellectual work (professional people and foremen).

*

II. School-education

1. Elementary school

2. Secondary schools. Folk high schools

3. Secondary schools (matriculated), Universities etc.

III. In the evaluation of *socio-economic level* the 3 social groups defined by the occupation of the father and generally recognized in Sweden were used.

Social group I. Owners and managers of large and middle-sized companies. Employees in responsible position — usually with university education.

Social group II. Owners of small businesses and employees in less responsible positions. This group also includes most owners of middle-sized farms.

Social group III. Workers, and men with small farmyards.

IV. In the description of the *degree of urbanity* 4 classes were recognized.

1. Country

2. Small country towns (at least 500 inhabitants).

3. Towns with a population of less than 100,000 inhabitants.

4. Towns with a population of more than 100,000 inhabitants.

QUESTIONNAIRES SENT TO MOTHERS OF PROBANDS

The questionnaires sent to the mother's included questions on:

1. Incidence etc. of diabetes among relatives.

2. Number of relatives of different types.
3. Ages of probands' parents and grandparents.
4. Weights and heights of parents.
5. Birthweights of the proband and his sibs.
6. Mother's age at the menarche.
7. Mother's age at first parturition.

In series A 88.8% of the mothers co-operated, the corresponding figures for series Br and Bc being 90.3% and 74.9%.

STATISTICAL METHODS

Arithmetical means (m), standard deviations (SD), standard errors of single deter-

minations (SE), and coefficients of correlation (r) were calculated according to standard statistical methods.

The significance of a difference between two means was estimated with Student's t -test.

A difference was said to be almost significant (*), significant (**) and highly significant (***) when the corresponding levels of probability were 0.05–0.01, 0.01–0.001 and less than 0.001, respectively.

Correlations built upon skewed distributions or when one variable contains only 3 or 4 classes were marked with $\square$.

Arithmetical means, standard deviations and distributions of all data of series B are given in Appendix II, Table 1.

IV. GENETIC-STATISTICAL ANALYSIS

GENERAL CONSIDERATIONS ON THE INHERITABILITY OF DIABETES MELLITUS

Familial factors are of importance in the causation of diabetes, as has been convincingly shown by the increased frequency of diabetes among relatives of diabetics (ALLAN, 1933, PINCUS & WHITE, 1933, GRUNNET, 1957, STEINBERG, 1959, 1961).

This increased frequency may be explained by genetic factors or by pseudoheredity, the latter produced by environmental influences such as familial dietary habits. Strong evidence for the genetic alternative has been produced by investigations of twins (THEN-BERG, 1939).

*

The nature of the inherited factor may be variable, and the following possibilities deserve consideration:

1. A uniform gene whose penetrance may be dependent upon environmental as well as constitutional factors. A possible alternative is then that of a mild form of the disease in heterozygotes and a more severe form in homozygotes.

2. Various genes with similar or different patterns of transmission.

3. A common mutant gene whose penetrance is dependent mainly on hereditary factors.

*

In the evaluation of these alternatives the following considerations should be borne in mind.

- a. If diabetes, independent of type of manifestation, is present in such proportions among the relatives of diabetics as may be expected according to one Mendelian type of inheritance, it will argue for a uniform gene.

In the calculation of the gene frequency, the fact that penetrance is lower in the lower age classes must be taken into account. It does not seem probable that the frequency of manifestation ever reaches 100 % in an unselected group.

- b. In view of the frequency of manifest diabetes a recessive inheritance by a uniform gene must presuppose a fairly high frequency of the gene for diabetes.

One should then, after correction for age, observe a frequency of diabetes among parents of diabetics, which though lower, is of the same order as that among sibs of diabetics.

- c. If diabetes is caused by different mutant genes with a recessive manifestation, the frequency of each of the different genes for diabetes would be lower, which would imply that the frequency of manifestation among the parents would decrease relatively more than among the sibs, for with an extremely low gene frequency the incidence of homozygosity among sibs will be 25 % as against 0 % for parents.

- d. If diabetes is caused by a gene with dominant manifestation, the frequency of diabetic parents and sibs will be chiefly the same after correction for the increasing frequency of the disease with age.

- e. Also if the familial occurrence of dia-

betes is due to a hereditary nature of factors favouring penetrance, the considerations set forth above will be applicable.

In view of possibly hereditary influences on endocrine differences between the sexes, one might expect a certain degree of over-morbidity among relatives of the same sex as the diabetics.

*

In previous systematic investigations of the frequency of diabetes among relatives of diabetics it has proved difficult to correct the frequency of the disease for differences in age at onset in a random selection of diabetics. This difficulty has been avoided by some investigators by comparing the frequency of the combinations: diabetic + diabetic, diabetic + non-diabetic, and non-diabetic + non-diabetic among the parents of diabetics. Supposing a recessive pattern of inheritance and random mating, the frequency of these combinations should be $p^2 : 2qp : q^2$ (the frequency of the diabetes gene is called p and that of the corresponding normal allele q). In these investigations the distributions obtained have been compatible with a completely recessive inheritance and a gene frequency of about 0.20, as pointed out by STEINBERG & WILDER (1952) (For survey of materials studied see STEINBERG, 1961). The figures in these investigations are consistent with a dominant inheritance only if the degree of penetrance is fairly low.

PURPOSE OF ANALYSIS

The purpose of the analysis of the frequency of diabetes in different groups of relatives of the probands in series A and B was to find the best possible numerical expression for the risk of a relative of a diabetic being such a diabetes gene carrier as to be able to develop manifest diabetes.

PLAN OF INVESTIGATION

It appears possible, theoretically, to calculate the incidence of genic aberrations with varying penetrance at different ages if the pattern of inheritance is known and data on the following points are available:

1. Penetrance at different age levels in the population studied.
2. Familial structure at different age levels.
3. Reliability of the information obtained.

In addition the following conditions must be fulfilled:

4. Random mating in the population.
5. Marriage frequency and reproduction must be the same for different genotypes.
6. The phenotype must be distinguishable from other clinical pictures.

Under such conditions the expected frequency (L) in a group of proband families may be calculated in the following way: For each relative the expression $P_x \cdot s \cdot r$ is calculated, where P_x is the penetrance at the age level x of the relative, s the reliability of data on the different groups of relatives and r the risk in a certain type of inheritance and gene-frequency in the population of being such a gene carrier as to be able to develop manifest disease. These values can then be added for all the relatives to a given group of probands, L being $\Sigma P_x \cdot s \cdot r$.

1. PENETRANCE AT DIFFERENT AGE LEVELS

Since the age distribution of persons with manifest diabetes mellitus may have changed during the last decades, particularly since the introduction of insulin, and the increased expectation of life of the population, the age distribution must be based on recent examinations.

The age distribution of the disease in the population forming the basis of the present investigation, was known from the investigation by SILWER (1958), which was founded on a search of the hospital records in Kristianstads län from the years

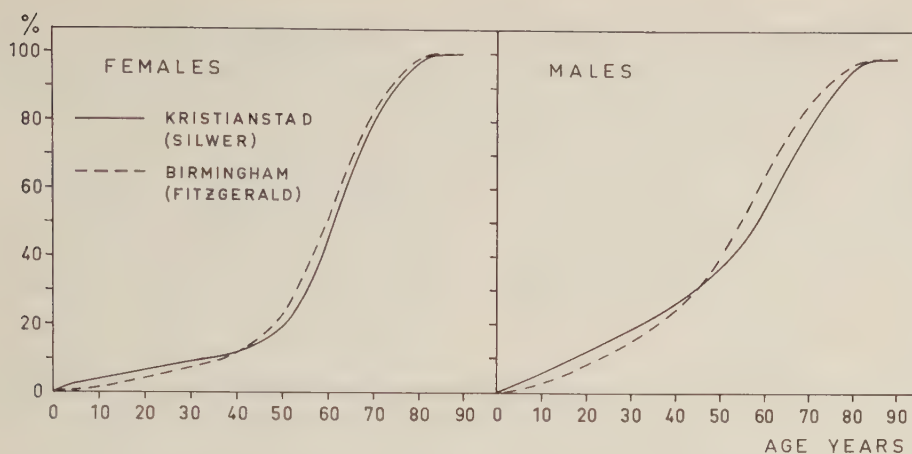


Fig. 1. Penetrance at different age levels, in per cent of maximal penetrance.

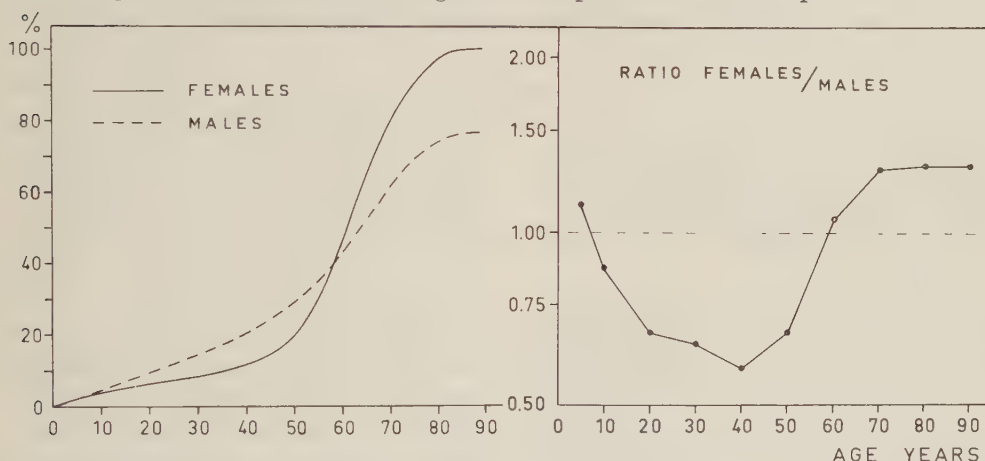


Fig. 2. Penetrance of male and female diabetics at different age levels, in per cent of maximal penetrance among females.

1944–1953 and on written enquiries among all doctors practising in that area during the same time.

The curves for both sexes in Fig. 1 were constructed on the basis of cumulative percentages of diabetics in whom the disease became manifest within 10-year age classes — see Appendix II, Table 2. Only those cases were included in which the disease made its first appearance during the latest 10-year period, *i.e.* 1944–1953, so that the curves are largely independent of the overmortality of those in

whom the disease occurs early in life. The general validity of the curves is seen on comparison with curves based on the distribution of newly discovered cases in Birmingham during the years 1949–1958 (FITZGERALD *et al.*, 1961). The slight difference between the curves may be due in part to the difference in the age distribution of the two populations.

The ratio between the risk of manifest diabetes occurring at different age-levels in males and females in SILWER's material is given in Fig. 2.

Table 7. Mean number of different types of relatives in series A, Br and Bc.

Type of relative \ Series	A	Br	Bc
Sibs of probands	2.24	2.18	2.66
Sibs of fathers	4.79	4.35	4.76
Sibs of mothers	4.37	4.34	4.63
Paternal first cousins	8.67	9.17	8.11
Maternal first cousins	7.78	8.29	7.90

Table 8. Number of children of males and females of series Br who developed manifest diabetes before the ages of about 70 (grandparents) and about 50 (parents), respectively.

Type of relative	paternal		maternal		grand-		father	
	grand-	grand-	grand-	grand-	father	grand-	grand-	mother
	father	mother	father	mother	father	mother	father	mother
Number of relatives	24	43	19	44	43	87	26	17
Mean number of children	4.76	6.07	4.44	6.18	4.63	6.13	2.38	4.13

Ratio between number of children:
grandmother:grandfather 1.32:1, mother:father 1.74:1.

Neither in series A nor in other series on record (STEINBERG & WILDER, 1952) did the occurrence of diabetes tend to vary with birth rank. The ages of the sibs and cousins are therefore normally distributed about the same means as those of the probands — though the range of variation of these two categories is somewhat larger than that of the probands, but not to such an extent as to influence the degree of penetrance — particularly since the curves of both sexes in the region of 0–40 years may be regarded as linear.

In order to obtain corresponding figures for the risk at the age levels of parents and grandparents, the duration of the observation period was noted, *i.e.* the present age or, if the person had died, the age at death. At these age levels the curves can hardly be regarded as linear. The groups of parents and grandparents were therefore

divided into 4 equal parts according to the duration of observation. Within every fourth part the mean age was calculated and the corresponding degree of penetrance was read from the curves in Fig. 1. The mean of the 4 values found was regarded as the degree of penetrance at the age level.

Thus, the expected penetrance, expressed in per cent of maximal penetrance, was calculated for different types of male and female relatives of the probands in series A and B as well as of the probands in series B. The maximal penetrance — $P_{\max}$ — is a value, whose order must be assessed with due allowance for the various possibilities of inheritance and gene-frequency and is obtained as the quotient of the number of diabetes found, divided by the expected number of diabetic gene carriers capable of developing the disease.

2. FAMILIAL STRUCTURE

The number of relatives of different types are given in Table 7.

3. RELIABILITY OF INFORMATION

The reliability of the data given may be expected to vary with the type of relative and it is regarded as being best concerning sibs and parents, and less good concerning sibs of the parents and cousins. The reliability of the reports given by the probands in series B can be assessed by comparison between the frequency of diabetes among the probands and among the sibs and cousins of the probands. In the same way the incidence of diabetes among the parents and the sibs of the parents can be compared. In the latter group better knowledge of cases of severe diabetes requiring insulin can be expected compared with cases of mild diabetes not requiring insulin. In addition, knowledge of relatives who had the disease earlier in life may be expected to be better than that of those in whom the disease developed later, *i. e.* recently. These assumptions were confirmed on examination of series B (Fig. 3). As to the parent's sibs, then, half of those with insulin-treated diabetes were reported as against one eighth of those not treated with insulin. Knowledge was least regarding the parents' sibs in whom the disease had appeared late and did not require insulin.

*

Supplementary information about the disease in the conscripts' relatives was obtained from the mothers of the persons in series Bc, where the incidence of diabetes was not known by the 18 year old conscripts. Of the 179 mothers who cooperated, 9 reported a total of 11 cases of diabetes among uncles, aunts and grandparents of the probands. This frequency

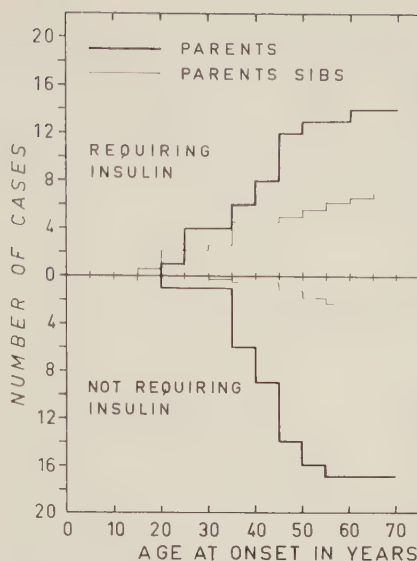


Fig. 3. Ratio between diabetics requiring and not requiring insulin at different age levels among parents and parents' sibs, as reported by probands.

was supposed to hold for all of the conscripts who were registered that year and who had not reported any heredity for diabetes. In the calculation 228 persons in series Br, 4 persons with manifest diabetes, and 179 persons in Bc whose mothers had given written answers, were subtracted from the total number of men registered, *i. e.* 2659. The number of relatives of diabetics in the group of conscripts registered that year was thus about 340, *i. e.* 13 per cent.

As far as series A is concerned, it may be assumed that the diabetic probands were more interested in the incidence of diabetes in the family and that they were therefore aware of most cases.

4. RANDOM MATING

Mating in the population studied was assumed to be random, at least concerning

the characteristics studied. This was supported to a certain extent by the fact that the geographical distribution of the birthplaces of the parents of the probands in series Br and those of series A belonging to the 6th registration district was largely the same as that of Bc.

5. REPRODUCTION OF DIFFERENT GENOTYPES

The calculation also requires that the reproduction and marriage frequency are the same for different genotypes.

Some authors have claimed an increased fertility among diabetics (for survey see ASCHNER & POST, 1956). In the present material, however, the numbers of cousins and of sibs of parents of relatives of diabetics did not differ appreciably from corresponding numbers in the normal population, *i. e.* series Bc. (Table 7)

Of particular interest in this respect was the agreement between the numbers of cousins, which may be regarded as an expression of the product of the factors marriage frequency and fertility.

6. INHERITANCE OF DIABETES

As was described above extensive evidence is available for the significance of genetic factors in the occurrence of diabetes.

Many investigations suggest a uniform gene and, particularly autosomal recessive inheritance seems to fit in with the distributions and frequencies found. The possibility of different types of diabetes with different modes of inheritance has, however, been proposed by other research workers, and it cannot be assumed with certainty that all cases of diabetes mellitus is due to the same genic aberration.

7. NUMERICAL EXPRESSIONS OF THE RISK OF BEING A CARRIER OF A GIVEN GENE

If random mating and identical reproduction and frequency of marriage of the genotypes can be assumed, it is possible to calculate with what probability different types of relatives of a given proband will be homozygous or heterozygous carriers of the proband's genes (HULTKRANTZ & DAHLBERG, 1927). The numerical expression of this probability was calculated for the diabetes gene for different gene frequencies in the population and assuming a dominant as well as a recessive mode of inheritance (See Appendix IV).

*

The investigation was based primarily on series A, which consisted of persons with early diabetes. If the frequency of diabetes among relatives of these persons is increased, the increase should be due to the same form of diabetes as in the probands.

The figures thereby obtained were checked in other materials. Differences between the values found and those expected were apparently due to diabetes with an aberrant genetic background.

In addition to the above mentioned procedures the frequency of the diabetes gene and the type of inheritance were estimated by investigation of the proportions non-diabetic + non-diabetic, non-diabetic + diabetic, diabetic + diabetic among parents of diabetics in series A.

Further, those members of series A and B were selected who had a diabetic parent whose mother or father was also diabetic. The grandparents were divided into those requiring and those not requiring insulin. It was assumed that the latter group might contain an increased number of heterozygotes with mild diabetes or, if different forms of diabetes inducing genes exist,

Table 9. Distribution of diabetic relatives in series A and B.

Type of relative	Series		
	Br	Bc	A
Brother	6		7
Sister	4		2
Father	26		8
Mother	17		2
Paternal uncle	19		10
Paternal aunt	15	1	5
Maternal uncle	11	2	5
Maternal aunt	12	1	3
Paternal grandfather	24	2	7
Paternal grandmother	44	2	7
Maternal grandfather	20	2	7
Maternal grandmother	48	1	8
First cousin	38		8

they would not be equally common in both groups.

In an attempt to assess the importance of exogenous factors, *e.g.* dietary habits, the frequency of diabetes was studied among married partners of diabetics.

RESULTS AND DISCUSSION

The number of relatives with diabetes in series A and B are given in Table 9. Table 10 gives the expected frequency (L) of diabetics among different types of relatives of probands in series A according to the formula: $L = \sum P_x \cdot s \cdot r$, described above.

Males and females were treated separately. In series A the $P_{\max}$ was strikingly high for males as compared with that for females in view of the known situation in the population. It appeared possible that in the families of the male juvenile diabetics there were genetically determined factors which particularly favoured the penetrance in males. The $P_{\max}$ for females was therefore considered to be more generally valid, for which reason, in the further calculations $P_{\max}$ for males was corrected

for the ratio between $P_{\max}$ for males and females in SILVER's material (Fig. 2).

A completely recessive mode of inheritance with a ratio of 0.15–0.25 between pathogenic and non-pathogenic alleles in the population studied seemed to best fit the observed values. A dominant inheritance with a gene ratio of the order of 0.05 and a degree of manifestation of about 20–30% also largely agreed with the number of diabetics found. However, the number of sibs expected would then be too small compared with that found.

*

The reliability of these calculations was checked in the following ways.

1. The number of diabetic probands and diabetic relatives of different types of probands in series B are given in Table 11, where they are compared with expected values for different assumed gene frequencies. The most useful values are those concerning the sibs, and the parents. As is clear from Fig. 3, knowledge of diabetes not requiring insulin in uncles and aunts was meagre so that it was thought advisable to correct the figures for the sibs

Table 10. Expected incidence of diabetes among relatives of 101 probands in series A assuming recessive inheritance, as well as dominant inheritance. (Series A consists of 119 probands, of whom 10 reported no heredity, 6 were able to give information on only one of their parents and were therefore excluded, and 2 pairs of the probands were brothers: this left 101 for further analysis.)

Males				Recessive					Dominant		
				E	1/4	1/5	1/6	1/7	1/100	1/20	1/10
A	B	C	D	F	0.61	0.78	0.94	1.09	0.36	0.31	0.27
Brother	1.12	14	7		3.8	4.4	5.0	5.6	3.0	2.7	2.5
Father	1	41.5	8		6.4	6.5	6.5	6.5	7.8	6.9	6.2
Uncle	4.58	41.5	15		18.3	17.9	17.5	17.3	18.1	18.7	19.1
Grand-father	2	80.3	14		15.5	15.1	14.8	14.5	15.2	15.8	16.2
Females											
				E	1/4	1/5	1/6	1/7	1/100	1/20	1/10
A	B	C	D	F	0.61	0.78	0.95	1.11	0.36	0.30	0.26
Sister	1.12	7	2		1.9	2.2	2.6	2.9	1.5	1.3	1.2
Mother	1	20.3	2		3.1	3.2	3.3	3.2	3.8	3.4	3.0
Aunt	4.58	20.3	8		9.0	8.8	8.7	8.5	8.9	9.1	9.3
Grand-mother	2	67.3	15		13.0	12.8	12.5	12.4	12.8	13.2	13.4

A. Type of relative.

B. Number of certain types of relatives per proband.

C. Penetrance at age level of type of relative given as percentage of maximal penetrance for each sex.

D. Number of known diabetics among relatives of given type.

E. Assumed diabetes gene frequency in population.

F. Penetrance among gene-carriers capable of developing diabetes on the assumption of different gene frequencies.

of the parents on the basis of the frequency of diabetes among parents. The data given by the probands in series Br on their grandparents were supplemented by information obtained from the mothers of the members of series Bc.

In the evaluation of the numbers of mothers and grandmothers with diabetes in series B correction must be made for the increased number of children in females with diabetes. Diabetic women at the 70-year age level have an increased number of grandchildren and consequently a greater possibility of being represented among grandparents of the 18 year old

conscripts. This also holds for the middle-aged mothers with diabetes. The number of children of parents and paternal and maternal grandparents of series B with diabetes is given in Table 8.

2. 48,000 males were born in Scania 1934–1942. 139 subjects out of these were exempted from military service owing to diabetes. At 20 years the penetrance in males was on the average 10% of $P_{\max}$.

On the basis of these figures the expected values given in Table 12 were calculated and compared with the observed number.

3. In SILVER's material the incidence of

Table 11. Expected incidence of diabetes among 2,659 probands in series B and their relatives compared with observed values assuming a recessive inheritance with a population gene frequency of $1/5$ — $1/7$ and dominant inheritance with a population gene frequency of $1/100$ and $1/20$.

Males					Recessive				Dominant	
					E	1/5	1/6	1/7	1/100	1/20
					F	0.78	0.95	1.11	0.36	0.30
A	B	C	D	D ₁	G	3.13 %	2.64 %	2.26 %	0.73 %	2.95 %
Proband	2659	9.6	6	6		8.0	6.7	5.8	1.9	7.6
Brother	3324	9.6	6	6		10.0	8.4	7.2	2.3	9.5
Father	2659	33.2	26	26		27.6	23.3	20.0	6.4	26.3
Uncle	11967	33.2	30	117		124.4	104.9	90.0	28.8	118.2
Grand-father	5318	60.4	44	90		100.5	84.8	72.7	23.3	95.6
Females										
Sister	3324	6	4	4		6.2	5.3	4.1	1.5	6.0
Mother	2659	19	17	14		16.2	13.7	10.6	3.8	15.7
Aunt	11967	19.5	26	63		73.0	61.6	47.6	16.9	70.7
Grand-mother	5318	70.0	92	120		116.5	98.3	75.9	27.0	112.8
Total			251	446		482.4	407.0	333.9	111.9	462.4

A. Type of relative.

B. Number of probands and different types of relatives.

C. Degree of penetrance at age level of relatives and expressed as percentage of $P_{\max}$ (i.e. $P_{\max}$ women in series A).

D. Number, known by probands in series Br, of diabetics among relatives of given type.

D₁ = D corrected in following ways:

- 1) Mothers and grandmothers for effect of large number of children — see table 8.
- 2) Grandparents with the supplementary data obtained from mothers in series Bc, see Table 9, assuming numbers of both sexes to be of equal size.
- 3) Numbers of uncles and aunts are calculated according to the occurrence of diabetes among parents with the assumption that each parent had on the average 4.5 sibs.

E. Assumed diabetes gene frequency in population.

F. Penetrance among gene-carriers capable of developing diabetes on the assumption of different gene frequencies.

G. Assumed maximal manifestation in per cent of population.

Table 12. Expected number of male diabetics born between 1934 and 1942 for different, assumed gene frequencies and modes of inheritance. (Number of males born during this period in Scania=48,000. Observed number of diabetics in military register=139. Manifestation among males at 19 years=10 % of $P_{\max}$).

	Recessive 1/5	Recessive 1/6	Recessive 1/7	Dominant 1/20
G	3.13	2.64	2.26	3.03
H	150.2	126.7	108.5	145.4

G. Assumed maximal manifestation in percent of population.

H. Expected number of diabetics.

Table 13. Maximal frequency of diabetes (age level 70—79 years) found by SILWER (1954) in town and rural populations compared with calculated maximal frequency in per cent of total population for different assumed gene frequencies and modes of inheritance.

	Morbidity age-level 70—79 (SILWER)		Recessive			Dominant
	rural	town	1/5	1/6	1/7	1/20
males	1.60	1.86	2.39	2.02	1.73	2.31
females	2.08	2.83	3.13	2.64	2.26	3.03

diabetes was highest in the 70—79 year age class — see Table 13. The differences between the figures for rural and town population may be due to a higher frequency of diabetes inducing genes in the latter, but is more likely due to an increased penetrance and more complete registration, especially of the elderly women and particularly those living in towns. The values may be compared with the expected morbidity for recessive as well as dominant inheritance and different assumed frequencies of the diabetes gene.

4. 91 of 101 probands in Series A had non-diabetic parents, while each of the remaining 10 had one diabetic parent. Since the degree of penetrance at the age level of the parents was about 35% for males and 20% for females, and assuming an autosomal recessive inheritance a probable proportion between the number of parental combinations of heterozygote + heterozygote: homozygote + heterozygote: homozygote + homozygote seems to be 68: 30: 3. Since this ratio also holds for $(1 - p)^2 : 2p(1 - p) : p^2$, the frequency of the diabetes gene (p) may be assessed as about 0.18.

The figures are compatible with a dominant inheritance and $P_{\max}$ about 30% if the gene frequency is assumed to be about 0.05.

5. The frequency of diabetic parents

with a diabetic mother or father was 3.6% for probands in series A and 3.7% in series B.

If the diabetic grandparents with known therapy in series B were divided into 60 requiring and 46 not requiring insulin, the frequency of diabetes among children was 3.5% and 3.8%, respectively.

The values obtained indicate, after correction for age, that about 15% of the children of diabetic parents will sooner or later develop diabetes and are well consistent with an autosomal recessive inheritance and a gene frequency of 0.15—0.20. The similar figures when the parents are requiring and not requiring insulin argue in some degree for a uniform diabetes gene and against the assumption that mild diabetes not requiring insulin should be more common in heterozygotes.

Here, too, a dominant inheritance with a gene frequency about 0.05 and $P_{\max}$ 30% is compatible with the values found.

*

As is apparent from the above comparisons, good agreement was found between the expected and observed values on the assumption of an autosomal recessive mode of inheritance and then best with an assumed gene frequency of 0.17 — 0.20 and a maximum penetrance of 60—70% in

Table 14. Risk at birth of being a homozygous diabetes gene carrier and risk at 20 years of age of developing diabetes during rest of life on the assumption of a recessive inheritance and a gene frequency of 0.20 in the population.

Type of diabetic relative(s)	Risk at birth of being a diabetes homozygote.	Risk at 20 of developing diabetes during rest of life.	
		male	female
Sib	0.35	0.18	0.25
Parent	0.20	0.10	0.14
Child	0.20	0.10	0.14
Grandparent	0.12	0.06	0.08
Uncle or aunt	0.11	0.05	0.07
First cousin	0.08	0.03	0.04
Grandparents on same side	0.20	0.10	0.14
Grandparents on different sides	0.33	0.17	0.22
Parent + grandparent on side of other parent	0.58	0.30	0.40
Parent + sib of other parent	0.54	0.26	0.35
First cousins on different sides	0.15	0.05	0.06
Parent + first cousin on side of other parent	0.36	0.16	0.21

male homozygotes and of 80–90 % in female homozygotes. STEINBERG & WILDER (1952) found a corresponding gene frequency of about 0.20.

A dominant inheritance with a gene frequency of about 0.05 and a maximum penetrance of about 25 % in males and of about 30 % in females could be an alternative but less probable interpretation of the observed values.

Assuming that the character is recessive, the values found would not argue against the assumption of a mild form of diabetes in a few heterozygotes, and then particularly in females, though the frequency of penetrance in these heterozygotes would be low. Neither can the possibility of an aberrant form of diabetes chiefly in elderly persons be excluded.

The material does not lend itself well to evaluation of the last two possibilities.

If the character were recessive, one might imagine that the pseudoheredity due to such exogenic factors as dietary habits

would probably be of less importance. The frequency of diabetes among married partners of the diabetics in series B — 3/172 among grandparents and 0/53 among parents, did not differ from that in the general population.

*

In the calculation of the risk of a given relative to develop diabetes, described in Table 14 and Fig. 4 the values given in Appendix IV are not absolutely accurate. It should also be taken into account that in the earlier generations there is a reduced risk of homozygosity among those who have attained a certain age but have not developed diabetes.

Since it was not possible to find out the incidence of diabetes in generations before that of the grandparents, which was probably low, these generations were treated as unknown.

As for the parents and grandparents,

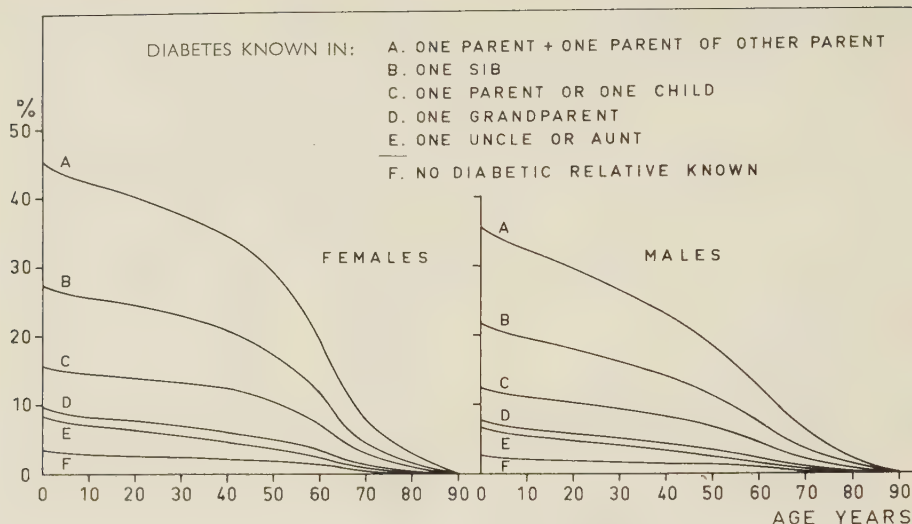


Fig. 4. Risk of developing diabetes during rest of life, calculated for different age levels and different known diabetic relatives.

they were regarded as being 30 and 60 years, respectively, older than the probands, the penetrance for the respective age levels being obtainable from Fig. 1.

No correction was made for non-diabetic sibs — in the present situation with relatively small numbers of sibs the values obtained are influenced only to a negligible extent by this factor.

CONCLUSION

The assumption of a uniform autosomal completely recessive inheritance fits in best with the frequencies of diabetes observed among different types of relatives of probands in series A and B. Assuming such an inheritance, the risk of different types of relatives to develop diabetes at various age levels can be calculated.

V. GROWTH AND DEVELOPMENT OF DIABETICS AND RELATIVES OF DIABETICS

PURPOSE OF INVESTIGATION

On the basis of clinical observations it has long been customary to recognize two types of diabetes, which have been called juvenile and adult diabetes according to age at onset. The former is said to occur preponderantly among individuals of slender body build, while the latter is described as being most common in association with overweight and as running a more benign course (HIMSWORTH & KERR, 1939).

Different modes of inheritance have been suggested for the two types (CAMMIDGE, 1928; GRUNNET, 1957). A point that has been widely discussed is whether diabetes is transmitted by a uniform gene or by different genes, and secondly, if a uniform gene is responsible, whether the homozygote would suffer from a more serious type of diabetes with an earlier onset than the heterozygote (HARRIS, 1950). The relatively higher incidence of adult diabetes in the families of juvenile diabetics argues for a uniform gene. Thus, in the present investigation the number of members with adult diabetes in the families of juvenile diabetics would agree with the proportion expected, if the pathogenic gene is uniform.

A question that then presents itself is whether juvenile diabetics in whom the disease has not yet become manifest are also of slender body build or whether the slenderness is evidence of the effect of the disease on some organs or systems particularly vulnerable during preadolescent and adolescent growth.

PLAN OF INVESTIGATION

In an attempt to elucidate these points measurements were made of the weights and heights of:

- a. diabetics at 13, about 18 and about 50 years of age,
- b. males at 13 and 18 years in whom diabetes developed within the next few years,
- c. varying types of relatives of approximately the same ages as in (a), of diabetics,
- d. age-matched controls.

In the groups about 18 years old the relative amounts of various types of tissue (skeletal, muscle and fat) were also assessed as well as the effect of diabetes heredity and the duration of manifest diabetes on these factors.

RESULTS AND DISCUSSION

The results are given in Tables 15–20 and in Fig. 5.

In order to check whether the increased rate of growth found was not due to differences in composition between series Br and Bc, height and weight at 18 years were calculated for series Br also with the assumption of the same distribution of occupations as in Bc. It is clear from Appendix I, Table 2, that the difference found in height and weight at 18 years between Br and Bc could not be ascribed to differences in occupation.

Neither could sociologic differences be-

Table 15. Weight and height at 13 years of age.

				Weight		Height	
		series	n	mean (kg)	SD	mean (cm)	SD
1	Matched controls, schoolregister	A	48	40.7	6.5	150.9	7.8
2		B	114	43.7	6.8	155.1	8.1
3		Bc	60	43.6		154.7	
4		B	85	42.7		153.8	
5	Diabetes known in Grandparent	Br	27	42.6		154.6	
6	Uncle or aunt	Br	17	43.1		154.2	
7	Parent or sib	Br	11	48.2		160.5	
8	Age at Onset <13 years	A	20	38.3		147.3	
9	=13 "	A	8	41.4		153.0	
10	>13 "	A	20	42.8		153.6	
diff. 1—2				t=2.65*		t=3.11**	
diff. (3+4+5+6)—7				t=2.46*		t=2.51*	
diff. 8—(9+10)				t=2.16		t=2.67*	

tween Br and Bc explain the difference between weight and height of relatives and non-relatives at 50 years — c. f. Appendix I, Table 4.

TENDENCIES IN PHYSICAL DEVELOPMENT OF RELATIVES OF DIABETICS

At the age of 18 (Table 16) and about 50 years (Table 20) the relatives of the diabetics tended to be taller and heavier than the controls. This tendency was most marked when a parent or sib was diabetic and was then discernible also in the 13-year old group (Table 15). This may be compared with WHITE'S (1960) report on accelerated growth between the ages of six and sixteen of children of diabetic mothers. Other investigators, for example HAGBARD, OLOW & REINAND (1959), found no overgrowth when children of diabetic mothers were observed up to 16. At 18 years the skeletal sturdiness factor as well as the fat-free weight of children and sibs of diabetics was advanced for age. No sure

tendency was found for relatives other than those referred to above.

The tendency to increased growth may be hereditary (GARN *et al.*, 1960) and possibly favour the penetrance of diabetes. If so, it may result in an over-representation of overweight subjects among the relatives of diabetics.

Overweight was most marked at 50 years (Table 20), which may be ascribable to a stronger influence of body fat on weight. This overweight was greatest, at least in females, when there was paternal diabetes. It seems reasonable to assume that the penetrance of diabetes is dependent to a higher degree on hereditary growth-promoting factors in males than in females, the risk of the disease developing in females also being increased by other factors, *e. g.* reproduction.

It is also believed that familial habits, *e. g.* over-eating, may result not only in overweight but also in a latent diabetes becoming manifest.

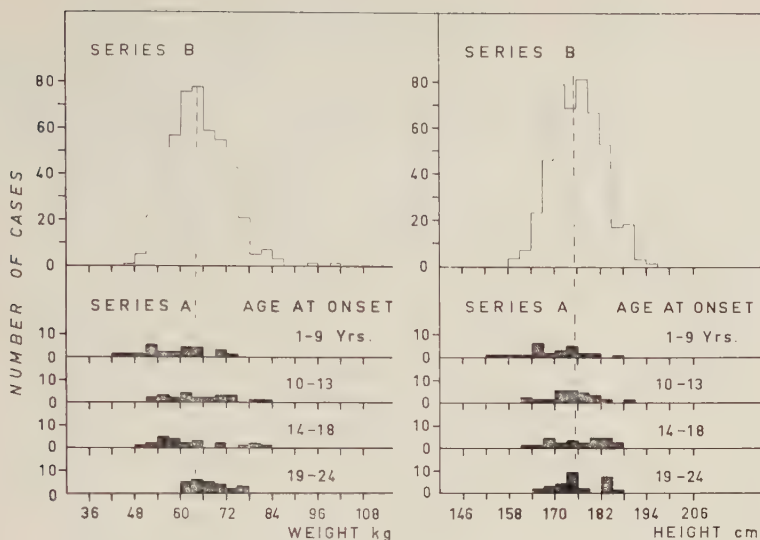


Fig. 5. Weight and height at induction in series A and B.

Table 16. Weight and height at induction.

		series	n	Weight		Height	
				mean (kg)	SD	mean (cm)	SD
1		A	96	63.2	8.2	173.8	7.3
2		B	467	64.3	7.5	175.6	6.5
3		Br	237	64.5		176.3	
4		Bc	230	64.0		174.9	
5	Diabetes known in						
6	Pat. grandparent	Br	68	63.9		175.5	
7	Mat. grandparent	Br	71	64.7		176.5	
8	Pat. uncle or aunt	Br	29	64.1		176.2	
9	Mat. uncle or aunt	Br	25	64.3		175.3	
10	Father	Br	26	65.0		176.4	
11	Mother	Br	17	64.2		177.9	
	Sib	Br	10	67.6		177.4	
12	Age at onset						
13	1—9 yrs	A	24	58.8		169.3	
14	10—13	A	24	64.4		175.0	
15	14—18	A	24	62.4		176.1	
16	19—24	A	24	67.1		175.1	
	matched controls	A	96	64.9		175.6	
	diff. 3—4			t=0.96		t=2.06*	
	diff. 4—(9+10+11)			t=1.18		t=1.96	
	diff. 12—16			t=3.25**		t=3.77**	
	diff. 15—16			t=1.25			
	Correlation between age at onset and weight (height)			r=0.37***		r=0.32**	
	Correlation between duration of diabetes and weight (height)			r=—0.37***		r=—0.35**	

Table 17. Length factor.

	series	n	Tibia		Radius	
			mean (cm)	SD	mean (cm)	SD
	A	109	39.7	2.6	25.8	1.8
	B	208	39.0	2.8	25.8	1.4
	Bc	103	39.0		25.7	
Diabetes known in						
Pat. grandparent	Br	26	38.6		25.7	
Mat. grandparent	Br	29	39.2		25.8	
Pat. uncle or aunt	Br	18	38.4		25.7	
Mat. uncle or aunt	Br	12	39.3		25.8	
Father	Br	10	38.2		25.8	
Mother	Br	5	41.4		27.3	
Sib	Br	7	39.7		25.6	
Age at onset						
1—9	A	30	38.6		24.9	
10—13	A	26	39.8		25.8	
14—18	A	26	40.2		26.0	
19—23	A	27	40.2		26.6	
Correlation between age at onset and length of tibia (radius)			r=0.21*		r=0.34***	
Correlation between duration and length of tibia (radius)			r=0.21*		r=0.36***	

TENDENCIES IN PHYSICAL DEVELOPMENT OF JUVENILE DIABETICS

There was a tendency to overweight of the 18 year old males who developed manifest diabetes within the following 5 years (Table 16). This tendency could not be accounted for by overweight. Owing to lack of age-matched controls, it was not possible to assess to what extent fat tissues, muscles or skeleton were responsible for this overweight, though some increase in the muscle and sturdiness-factors may be assumed.

The 13 year old group (Table 15), was too small to warrant comparison with controls.

*

Though most investigators have found overweight, overweight, and overmaturity of bones, in freshly diagnosed cases of

juvenile diabetes (WHITE, 1960) this rule is not without exceptions (DANOWSKI, 1957).

Increase in weight without increase in height may be compared with the tendency to early sexual maturity, as manifested by a lower age at menarche in girls who later on in life develop diabetes (WHITE, 1959). As shown by several investigators (for survey see TANNER, 1955), an early sexual maturity is preceded by a relatively high rate of increase of bodyweight, observable already during childhood. Until the age of 15 years this is accompanied by a corresponding increase in height, but not after the age of 18 years.

Some investigators (TANNER *et al.*, 1959) have found the urinary excretion of 17-ketosteroids to be increased in persons heavy for their height. This can be compared with the observation by WHITE (1959)

Table 18. Muscle and sturdiness factor and fat-free weight.

	series	n	Handgrip		Shoulder thrust		Shoulder pull		Condylar breadth		Fat-free weight	
			mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
1	A	107	43.3	7.3	53.2	11.3	37.2	7.6	9.54	0.45		
2	B	208	41.1	5.8	55.9	11.8	34.1	6.8	9.56	0.42	59.1	5.8
3	Bc	103	41.6		57.8		34.2		9.54		58.2	
4	Diabetes known in											
5	Grandparent	55	40.3		53.7		33.1		9.55		59.1	
6	Uncle or aunt	30	41.2		55.7		36.4		9.61		59.3	
	Parent or sib	22	41.7		55.2		34.4		9.69		61.8	
7	Age at onset											
8	1—9 yrs	30	38.4		43.7		34.3		9.31			
9	10—13	25	43.6		54.1		37.6		9.63			
10	14—18	25	44.3		55.0		35.6		9.60			
	19—24	27	47.5		61.1		41.6		9.64			
	Correlation between muscle- and sturdiness factor and duration of diabetes		—0.40***		—0.45***		—0.22*		—0.33***		Diff. 3—(4+5+6) t=1.46 0.2>P>0.1 Diff. 3—6 t=2.74 0.05>P>0.01	

Table 19. Fat factor.

			Skinfold back		Skinfold lat. chest		Skinfold abdomen		Weight minus fat-free weight as per cent of weight	
	series	n	mean	SD	mean	SD	mean	SD	mean	SD
	A	108	8.4	2.4	6.0	2.2	8.3	4.1		
	B	208	6.7	1.2	5.1	2.1	6.0	2.3	11.6	9.1
	Bc	103	6.6		5.1		5.8		12.0	
Diabetes known in Grandparent	Br	55	6.8		5.2		6.4		11.6	
Uncle or aunt	Br	30	6.7		5.1		6.1		11.1	
Parent or sib	Br	22	6.7		4.8		6.0		8.9	
Age at onset										
1—9	A	30	8.7		6.3		8.1			
10—13	A	25	8.3		6.0		8.7			
14—18	A	26	8.3		5.8		8.5			
19—24	A	27	8.2		5.9		7.8			
Correlation between fat-factor and duration of diabetes			r=0.12		r=0.09		r=0.01			

that the urinary excretion of 17-ketosteroids is increased at the onset of manifest diabetes, but seems to be reduced in the later course of the disease.

*

On the other hand, in the juvenile diabetics the values found for bodyweight, bodyheight, condylar breadth and muscle mass at about 18 years were below those noted in the controls, the differences tending to be largest when the disease had become manifest before the age of 10–13 years. The amount of body fat seemed to be normal, or, if anything, somewhat increased.

A tendency to underweight and underheight was also noted among the 13-year-old diabetics. In these, too, the degree of under-development appeared to vary with the duration of the disease.

The retardation of growth observed by several investigators (WAGNER *et al.*, 1942,

ENGEL, 1947, BERGQVIST, 1954 a, LEUPOLD, 1960) may be compared with retardation of skeletal maturation in diabetics (MORRISON & BOGAN, 1927) and late menarche in diabetic girls (BERGQVIST, 1954 c, JOSLIN *et. al.*, 1959).

On the other hand, bodyweight of the 50-year-old diabetics in whom the disease had not become manifest until after they had filled 20 years of age was, on the average, greater than normal, and also exceeded that of the relatives of diabetics referred to above.

*

A certain increase in growth prior to the appearance of diabetes may be attributable to increased endocrine activity, mainly with increased secretion of pituitary growth hormone and possibly of testosterone. These hormones would then not only cause the increased growth, but also favour the penetration of diabetes which in this investiga-

Table 20. Weight and height of parents (about 50 years old) of probands in series A and B.

	Series	Male			Female			
		n	weight mean (kg)	SD	height mean (cm)	SD	height mean (cm)	SD
1	No diabetic relative	A	91	77.7	10.3	173.8	5.3	
2		B	345	78.6	9.6	175.0	6.2	164.9 6.0
3		B	226	77.4		174.8		164.2 5.3 163.9
4	Diabetes known in	Br	23	81.1		175.8		
5		Br	38	80.4		175.2		165.2 164.7
6		Br	28	77.2		175.3		164.3
7	Themselves diabetic	Br	21	81.3		174.5		165.7
8		Br	11	80.2				
9		Br	10	82.3				
10		Br	14	77.9		175.2		163.0
diff 3—(4+5+6)		t=1.68 (0.1>P>0.05)			t=2.13 (0.05*>P>0.01)			

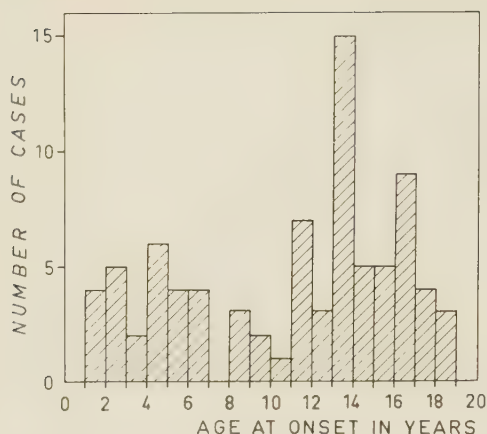


Fig. 6. Age at onset in series A.

tion was highest at 13 years of age — see Fig. 6 — an observation coinciding with that of most other workers (WHITE, 1959, CUTTLE & MACLEAN, 1947), who have found a maximal manifestation at 11 in girls and at 13 in boys.

Since the capacity of growth hormone and testosterone to exert their effects is apparently to some extent dependent on an

adequate production of insulin, (MILMAN *et al.*, 1951; SCOW & CHERNICK, 1960; SIREK & BEST, 1953) it seems reasonable that the retardation of growth of young juvenile diabetics is due to the successive reduction of endogenous insulin production some years after the onset of the disease and before the puberal growth spurt.

CONCLUSIONS

Judging from the observations set forth above,

- a. growth of young male diabetics is retarded, particularly of those in whom the disease appears before puberty,
- b. young males tend to be overweight before the disease becomes manifest,
- c. factors responsible for this overweight assumedly also favour the manifestation of the disease, and
- d. there appears to be no reason to assume any difference in the mode of inheritance between juvenile and adult diabetes on constitutional grounds.

VI. BIRTHWEIGHT OF YOUNG DIABETICS AND RELATIVES OF DIABETICS

PURPOSE OF INVESTIGATION

- a. To study the birthweight of juvenile diabetics.
- b. To study the birthweight of children of parents who later develop diabetes.
- c. To study the birthweight when relatives other than the parents have diabetes.
- d. To ascertain to what extent the overweight of children of women who later develop diabetes is due to the relatively large birthweight of children with a higher birth number.
- e. To ascertain to what extent the overweight of the infants is related to any overweight of the mothers who later develop diabetes.

PLAN OF INVESTIGATION

It has been observed in previous investigations (MOSENTHAL & BOLDUAN, 1933, PYKE, 1956, FITZGERALD et al., 1961) as well as in the present study, (See Table 8) that women who develop diabetes have, on the average, born more children than women in the rest of the population. Since birthweight has been found to increase with birth number (von WACHENFELDT, 1935, NAMBOODIRI & BALAKRISHNAN, 1959) a higher birthweight of the children of prediabetic females may be ascribed partly to multiparity.

In this investigation a correlation was

found between birthweight and overweight of the mother (See Appendix III, Table 1) which can be compared with the similar observations of ODELL & MENGERT (1945), GILBERT (1949), PIRART (1955).

As shown in Table 20, women who were diabetic at 50 years were overweight. In view of the general tendency of diabetic gene carriers to be overweight, a female overweight at 50 years may be related to an overweight during the childbearing years. It is clear from Table 21, however, that the overweight of the middle-aged women also varied with the number of children they had born, c. f. PYKE & PLEASE (1957). It was therefore considered necessary to ascertain whether the increase in birthweight of infants born of mothers who later developed diabetes may be due to the overweight caused by multiparity or to overweight *per se*.

*

The collection of data on series A and B was described in Chapter III. To elucidate the problems set forth above the following groups in these series were studied regarding birthweight and concerning the probands born at obstetrical clinics, also length at birth.

1. Children who developed diabetes before the age of 25 years.
2. Children who were sibs of juvenile diabetics.

Table 21. Correlation between number of children and weights of parents (Series B).

Number of children	1	2	3	4	5	6	7	8	9	10
Mother's mean weight (kg.) n	65.2 45	66.1 48	67.2 65	66.8 39	71.3 37	67.1 29	73.3 42	74.9 21	69.3 10	77.7 40
Father's mean weight (kg.) n	79.5 39	76.8 64	78.5 45	79.8 48	75.4 24	74.8 24	78.5 37	72.1 28	70.8 10	79.0 23

Correlation between mother's weight and number of children: $r=0.17$
Correlation between father's weight and number of children: $r=0.03$

3. Children of mothers who later developed diabetes.
4. Children of fathers who later developed diabetes.
5. Children with maternal heredity for diabetes.
6. Children with paternal heredity for diabetes.
7. Children without known diabetes in the family.
8. Children with different numbers of sibs.
9. Children of non-diabetic parents of increased weight and height at 50.

*

In series B the number of sibs was known, but not the birth rank of the probands or the weight of the mothers at the time of delivery. Therefore, in order further to elucidate the relationship between birthweight, and birth rank, and mother's weight, data were also collected on all children born at the Department of Obstetrics in Kristianstad in 1941 and at the Department of Obstetrics in Malmö 1960, which are hereinafter referred to as series K and M, respectively. Further, data were used on infants born at the Department of Obstetrics in Lund between 1911 and 1930 (infants of primiparae between 1900 and 1922)

(LUNDH, 1925, v. WACHENFELDT, 1935). These infants will be referred to as series L. Series L and K were collected from areas of similar social structure as series B, while series M was derived from a large town. Series M was partly chosen because the weights of the mothers in the other series had generally not been noted in the records.

The data on the probands in series A and B refer to boys only, while the corresponding values in series K, L and M, and for the sibs of the probands in A and B, were calculated independently of sex.

The differences between the weights of the boys and the girls in series K and M and L were 108 g., 96 g. and 118 g., respectively. The differences with sex correspond well with those found by other investigators (See BAKWIN & BAKWIN, 1934, ENGSTRÖM & FALCONER, 1960). In the calculations birthweights of less than 2000 g. and corresponding lengths were not included in series K and M — these number represented 1.7 % and 1.8 %, respectively. The corresponding limit for series L was 2,500 g. with the exception that none of the children of primiparae were excluded. Neither were twins included, which represented 1.9 % (19/994) of the deliveries in series K and 0.6 % (19/2978) in series M.

Table 22. Birthweight and birthlength series A and B.

	Series		Weight			Length		
			n	mean (kg.)	SD	n	mean (cm.)	DS
	A		93	3.65○	0.61	249	51.18○	2.17
	B		369	3.54○	0.57			
	Bc	prob.	186	3.54○				
	Bc	sib	218	3.57●				
	A:	matched controls	50	3.57○				
Diabetes in								
Mother	Br	prob. sib	12	3.95○		7	52.57○	
			33	3.80●				
Father	Br	prob. sib	19	3.71○		13	51.54○	
			34	3.70●				
Mat. relative	Br	prob. sib	71	3.60○		43	50.95○	
			96	3.72●				
Pat. relative	Br	prob. sib	67	3.44○		36	50.89○	
			92	3.51●				
Proband	A		93	3.65○				
Sib	A		135	3.66●				
>3 sibs	B		53	3.78○		40	51.95○	
Mat. wt>75 kg.	B		49	3.74○		35	51.54○	
Mat. ht>170 cm.	B		22	3.64○		16	51.88○	
Pat. wt>85 kg.	B		50	3.54○		31	51.29○	
Pat. ht>179 cm.	B		56	3.54○		43	51.14○	

○ = only boys.

● = boys and girls.

RESULTS AND DISCUSSION

The birthweights in the above-mentioned groups of Series A and B are given in Table 22. The relation between the birthweights of the children and the bodyweights of the mothers in series M and the birth rank in series K, L and M are summarized in Tables 23 and 24, respectively. The relation between birthweight and number of sibs in series B is given in Table 25 and the weights of the mothers

in series B is related to their productivity in table 21.

*

Many authors have observed the birthweight of children of prediabetic mothers to be increased (MILLER, 1945, MOSS & MULHOLLAND, 1951, JACKSON, 1952, PIRART, 1955). This increase has been ascribed partly to constitutional factors which is supported by the observation that even when the father was a diabetic or prediabetic a certain increase in birthweight of

Table 23. Comparison between mother's weight and birthweight of child (series M).

Mother's weight kg	Birth-rank	1			2			3—		
		n	n as % of total	mean (kg.)	n	n as % of total	mean (kg.)	n	n as % of total	mean (kg.)
45—49		6	0.5	3.08	3	0.3	2.82	4	0.7	2.72
50—54		40	3.3	2.74	30	3.5	2.97	19	3.3	3.10
55—59		129	10.5	3.12	83	9.5	3.16	49	8.5	3.17
60—64		249	20.3	3.26	187	21.7	3.35	105	18.3	3.40
65—69		283	23.0	3.39	168	19.5	3.51	101	17.6	3.38
70—74		232	18.9	3.45	149	17.3	3.63	110	19.1	3.56
75—79		138	11.2	3.57	128	14.9	3.62	83	14.4	3.72
80—84		70	5.7	3.53	55	6.4	3.69	48	8.3	3.45
85—89		40	3.3	3.64	32	3.7	3.71	22	3.8	3.76
90—94		25	2.0	3.78	13	1.5	4.00	12	2.1	3.66
95—		16	1.3	3.85	14	1.6	3.90	22	3.8	4.01
Total		1228			862			575		

Table 24. Birth weight and birth rank (Series L, K and M).

Birth rank	Series L		Series K				Series M		
	n	weight ¹ (mean)	n	n as % of total	weight ² (mean)	length ² (mean)	n	n as % of total	weight ² (mean)
1	7000	3.35	475	47.8	3.44	50.4	1324	43.8	3.35
2	3577	3.59	258	26.0	3.58	50.9	969	32.1	3.47
3	2920	3.62	111	11.2	3.63	51.0	472	15.8	3.46
4	1774	3.68	60	6.0	3.73	51.5	169	5.6	3.48
5—6	1973	3.71	50	5.0	3.80	51.7	90	2.6	3.42
7—9	1215	3.75	28	2.8	3.71	51.2	9	0.3	3.66
10—	531	3.83	12	1.2	3.85	52.9			
Total	18990		994				3033		

¹ All firstborns included — at higher birth rank, birthweight <2,500 g and twins excluded.² Birthweight <2000 g. and twins excluded.

Table 25. Birthweight and number of sibs in Series B.

Number of sibs	n	weight mean
0	40	3.45
1	95	3.57
2	90	3.58
3	39	3.52
4	24	3.75
5—	33	3.84

Birthweight <2000 g. and twins excluded

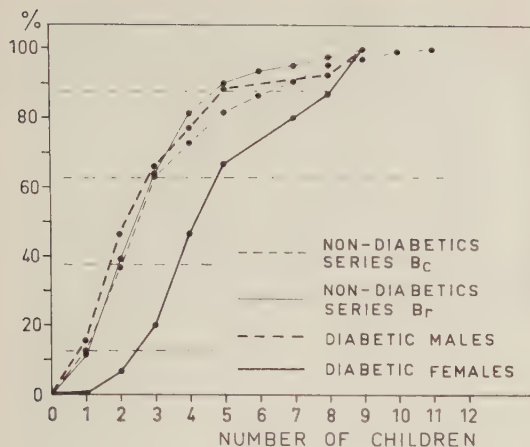


Fig. 7. Cumulative curve for parity of diabetic women, aged about 50, compared with normal curves.

the children has been demonstrable (JACKSON, 1952, SIEGELER & SIEGELER, 1960).

It appears that earlier investigators did not correct their results for multiparity and overweight of women who will develop diabetes.

After arrangement of the diabetic and non-diabetic mothers in series B into 4 equal groups according to the number of children they had born and construction of a cumulative diagram (Fig. 7), a difference was found between the diabetic and non-diabetic women, in that the number of children born by the women, diabetic at 50, in each quarter was larger than the corresponding number for the non-diabetic group. For each quarter of the 2 groups the weights corresponding to the found number of children was calculated from Table 24 and the mean of the differences between these weights was taken as a measure of the overweight ascribable to the larger number of children. The correction was made on the basis of values obtained from the analysis of series K, whose values roughly coincided with those of series L. Series M, which was derived from a population of different social structure, showed a somewhat different

pattern, for birthweight did not continue to increase after the second child.

It is clear from Fig. 7 that the birthweight of the child of the women who later develop diabetes should be corrected downwards by about 100 g. owing to multiparity of the mother.

On analysis of series M the infant's overweight at birth was found to be correlated, independently of birth rank with the weight of the mother at the time of delivery — See Table 23. The mother's weight at the time of delivery may be regarded as proportional to that before pregnancy. For it has been shown that the increase in weight during pregnancy is not related to the weight before pregnancy (IHRMAN, 1960). Neither does this increase in weight appear to be related with parity. Since it was not known with certainty to what extent the overweight of the diabetic women was due to increase in weight before age at delivery, or increase in weight between the age at which they had their children and 50 years, no correction could be made with certainty. An increase of 5 kg. in the bodyweight of the mother, as measured on admission, corresponded to an increase of

	Number of children		Corresponding birthweight	
	Diabetic	Non diabetic	Diabetic	Non diabetic
	Females		Females	
I	2.5	1.0	3.60	3.44
II	3.7	2.0	3.70	3.58
III	4.8	2.9	3.78	3.62
IV	7.1	6.5	3.76	3.76
Mean	4.5	3.1	3.71	3.60

about 100 g. in the weight of the child, independently of birth rank (Table 23).

One might imagine that both the parity and the weight of the mother are dependent on the age of the mother and that the differences observed are due to increased birthweight ascribable to the higher age of the mother. In series L (LUNDH, 1925, WACHENFELDT, 1935), no correlation was found between the age of the mother and the birthweight of the child. Nor was any such correlation found in the other series.

As a cause of overweight common to the mother and the child at birth the state of nutrition of the mother may be considered and is believed to influence birthweight to some degree (for survey see ABOLINS, 1961). This factor cannot be assessed in the present investigation, but it was probably of less importance in this material emanating from a generally well-nourished population.

Many investigators, BAKWIN & BAKWIN (1934) for example, have found a higher birthweight when the parents belong to a higher socio-economic level. This may be related to nutrition but seems to be independent of other factors referred to above. Some sociologic differences exist between diabetics and the normal population, as was discussed in Chapter II and is demonstrated in Appendix I. The material, however, was too small for an analysis of this influence upon birthweight, which was considered of less importance in the present investigation.

One might suspect that the overweight observed when the father is a future diabetic is only a consequence of the correlation between the weights and heights of the parents (Appendix III, Table 1). It is clear from Table 20, however, that the weights and heights of the wives of diabetics in the present material did not deviate from normal.

The 18 year old males who developed

diabetes before the age of 25 showed an increased skeletal and muscular development for age at 18 years (Chapter V). It is clear from Appendix III, Table 1 that birthweight was related to skeletal and muscle factors in 18 year old males.

The overweight at birth was, however, not directly proportional to the increased risk of development of diabetes owing to increased rate of growth. For the birthweights of the juvenile diabetics were the same as those of their normal sibs. Children with a low birthweight tended to develop the disease at the same time as those with a high birthweight — as a matter of fact there was, if anything, a tendency of those with a lower birthweight to develop the disease earlier ($r = 0.20$).

Length at birth generally varied with birthweight, so that the overweight of prediabetic parents as well as of children with a high birth number was probably due to a general increase in growth and not only to an isolated change of, *e. g.* fat or fluid.

No overweight or underweight was found among probands when more distant relatives were diabetic.

CONCLUSION

A child has a tendency to be overweight at birth if the mother develops diabetes later in life. This overweight is, however, due partly to the larger number of children born by the prediabetic women, since the overweight of the child at birth appears to be related to its birth number. Further, the weight of the child is possibly correlated with the overweight of the prediabetic mother, the maternal overweight appearing to influence the birthweight of the child.

If the father or sibs are diabetics, the overweight at birth will be less marked and will be of the same order as that for persons who will later develop diabetes.

VII. INTELLECTUAL ENDOWMENTS OF YOUNG DIABETICS AND YOUNG MALE RELATIVES OF DIABETICS

The intellectual endowments of diabetic children has received wide attention. Some authors have found no differences between diabetics and controls, others have found diabetics to be over-intelligent or under-intelligent for age (For survey see DĄNOWSKI, 1957).

Below a comparison is given of the scores achieved by diabetics, non-diabetic relatives of diabetics, and non-diabetic controls at tests performed at induction (Table 26).

The intelligence level of the 18 year old males who had diabetes mellitus or developed the disease within the following 6 years was found to be higher, though not significantly, than of age-matched controls.

No difference was found between the relatives of diabetics and the controls. The

differences obtained between different types of relatives is probably due to a correlation between the intelligence of the proband and his knowledge of the disease in other members of the family.

The intellectual level did not seem to vary with the duration of the disease.

Series A and B are not strictly comparable because of modifications of the tests during the years in question, and especially because the level of the results of the test were noticeably low in 1959 (See Table 6).

*

The value of the tests should not be over-estimated. The difference found might have been due to an increased degree of

Table 26. Results of intelligence tests (mean score).

	n	mean	SD
Series A	96	5.24	1.95
Age at onset of diabetes (yrs)			
1—9	24	5.38	
10—13	24	5.00	
14—18	24	5.67	
19—23	24	5.04	
Matched controls	96	4.73	
Series B	465	4.49	1.75
Diabetes known in:			
Grandparent, uncle or aunt	165	5.03	
Parent	44	4.34	
Sib	19	4.21	
Non-relatives	250	4.26	

Diff: Series A and its matched controls: $t=1.82$, $0.10 > P > 0.05$

penetrance and an earlier manifestation of the disease in larger towns and in certain sociologic group (c. f. Chapter II). While the population of Malmö represents 25 % of that of Scania, the diabetics living in

Malmö represent 30 % of series A. As is apparent from Table 7, the degree of urbanity as well as socio-economic level is correlated with the results of the intelligence tests.

VIII. INTRAVENOUS GLUCOSE TOLERANCE TEST

The purposes of the investigation were:

- A. To appraise the value of the intravenous glucose tolerance test with rapid injection of glucose as a measure of the risk of young males developing diabetes mellitus, as well as to appraise the effect of priming with adrenal glucocorticoids on the shape of the glucose curve.
- B. To assess the effect of total body volume and the ratio between different tissues (skeletal, muscle and fat) on the shape of the glucose curve.

COMMENTS ON METHODS

REMARKS ON INTERPRETATION OF GLUCOSE TOLERANCE TEST

In the beginning of the investigation the rate at which the blood sugar fell within the volume in which the glucose was initially distributed was taken as a basis for evaluating the risk of the development of diabetes, as well as for differentiating different tissues as to their influence upon the glucose curve. The effect of other factors on this fall must therefore be defined as accurately as possible.

Some factors which independently of the type of tolerance test might disturb the course were assumed to be:

- a. Physical fitness.
- b. Physical exertion just before test.
- c. Infections and other forms of exogenous stress.

- d. Psychic stress.
- e. Dietary habits, particularly carbohydrate intake the last few days before the examination.
- f. Diurnal rhythm.

a. *Physical fitness.* The degree of physical fitness of the young males varied — they had all been in the armed forces 1–60 days before the glucose tolerance test was performed. Also heaviness of the work in the previous occupations of the recruits varied. Many of them had come straight from school, where they had been preparing for their final examination and had had no time for physical exercise. Since the males were all about 19 years old, and apparently healthy the possibility of decreased glucose tolerance because of prolonged physical inactivity (BLOTNER, 1945) can be ignored.

The state of physical fitness might have improved with the number of days the men had been in the armed forces, for which reason the blood sugar level was studied for any correlation with the number of days that had elapsed since they had been enlisted. It was found that the fall in the blood sugar level tended to be more rapid with the duration of military service (see Table 27), though allowance must be made for a certain unevenness of the distribution of the material according to physical fitness. The glucose tolerance curve was not found to vary with the type

Table 27. Correlation coefficients between results of glucose tolerance test and

A: factors possibly stimulating increase of muscle volume and strength

B: pulse rate

		Blsr ₂₀ n=203	Blsr ₄₃ n=202	Total index n=202
A	Number of days after enlistment	-0.22	-0.15	0.04
	Manual labour in earlier occupation	-0.00□	-0.01□	-0.05□
B	Pulse-rate	-0.00	-0.07	0.08

For evaluation of significance, see Appendix V

of work the subjects had been doing, *i.e.* heavy manual labour or light work (Table 27).

*

b. Physical exertion just before test.

Physical exertion is believed to increase the rate of uptake of glucose even in the absence of insulin — probably by formation of a humoral factor (GOLDSTEIN *et al.*, 1953, GOLDSTEIN, 1961) and a relative “anaerobiosis” (RANDLE & SMITH, 1958). Thus, following severe physical exertion a lower or flatter glucose tolerance curve has been obtained (STRANDELL, 1934).

In the present investigation most of the subjects were examined in the bed in which they had been lying during the night. 54 of them had, however, come to the examination room the same morning, but they had avoided all unnecessary physical exertion that morning, and they had rested for at least 2 hours before the examination. No differences were found between the mean values of this group and that of the remainder.

*

c. Infections and other forms of exogenous stress. Before the examination the subjects were examined and questioned

whether they had had any recent infections which has been shown to rise the blood sugar level (BERG, 1926, LAWRENCE & BUCKLEY, 1927, TUNBRIDGE & ALLIBONE, 1940) and if they had, the examination was postponed. All together 3 had been on the sick-list the week before the examination because of infections of the respiratory tract, but they had returned to duty before the time of the examination — the previous infections do not appear to have influenced the blood sugar level.

Recruits are usually vaccinated against smallpox the first week after they have enlisted — in 2 of the men the glucose tolerance test was postponed because of marked reaction to the vaccine.

*

d. Psychic stress. The first few weeks of military service often imply a certain psychic stress, which is believed to raise the blood sugar (CANNON, 1947). In addition, venous puncture for the test undoubtedly implies a psychic strain for many, probably causing an increase in the pulse rate, which was therefore measured both immediately before and after the glucose tolerance test. It is, however, clear from Table 27 that no signs of a correlation were

demonstrable between pulse rate and the results of the glucose tolerance test.

*

e. *Dietary habits, especially carbohydrate intake at the time of the examination.* — On the days before the examination the men received their ordinary ration, which was considered to contain sufficient carbohydrate to exclude the possibility of the glucose tolerance test being influenced by carbohydrate deficiency (MALMROS, 1928, CONN, 1940, WILKERSON *et al.*, 1960). The possibility of a high carbohydrate diet resulting in increased tolerance has been suggested by some authors (SWEENEY, 1927) but denied by others (GOLDBERG & LUFT, 1948, TUNBRIDGE & ALLIBONE, 1940) — this possible source of error was ignored. The men were instructed not to eat during the last 12 hours before the examination. They were also requested not to smoke during this period, it having been shown by LUNDBERG & THYSELIOUS-LUNDBERG (1931) that smoking tends to raise the blood sugar.

*

f. *Diurnal rhythm.* There is probably a diurnal rhythm of the blood sugar level and especially of the tolerance for exogenous glucose. This rhythm may be due to the assimilation and dissimulation phases of the liver (FORSGREN, 1935). The tolerance tests were performed between 7.30 and 10.30 a.m. The results of the glucose tolerance test were not found to vary with time within these limits.

COMPARISON BETWEEN ORAL AND INTRAVENOUS GLUCOSE TOLERANCE TESTS

Circumstances allowed the choice between an oral tolerance test and an intravenous test with rapid injection of glucose, but not an intravenous test with slow infusion of glucose.

Each of the two methods available have

certain advantages and disadvantages. They probably differ in the following respects:

- g. Duration of uptake of glucose.
- h. Hepatic uptake and outflow of glucose.
- i. Renal excretion of glucose.
- j. Secretion of insulin and consequent increase of factors raising the blood sugar level.

*

g. *Duration of uptake of glucose.* — The absorption of glucose on oral administration varies and seems to be modified, among other things, by the rate of gastric emptying (WATSON, 1937, EVENSON, 1942), intestinal peristalsis (CUMMINS & ALMY, 1953), dilution of glucose in the intestines (CUMMINS & JUSSILA, 1956, ANNEGERS, 1961), and the capacity of the active absorption process (CRANE & KRANE, 1956, CRANE, 1960). These factors, which are difficult to assess, are completely avoided by intravenous injection of the glucose.

A disadvantage of the oral test, as far as the present investigation is concerned is also the fact observed by DISCHE *et al.* (1958) that the peak of the tolerance curve is probably reached quicker in persons of heavy bodybuild, while obesity *per se* seems to be combined with a retardation of the absorption of glucose.

*

h. *Hepatic uptake and outflow of glucose.* According to most authors (SOSKIN & LEVINE, 1952, SEARLE & CHAIKOFF, 1952), the outflow of glucose from the liver falls to low values if the blood sugar level is elevated, and returns to normal again with the falling blood sugar level. In manifest and latent diabetes the hyperglycaemia does not seem to be accompanied by a normal fall of the hepatic glucose outflow (SOSKIN & LEVINE, 1952, ISSEKUTZ *et al.* 1960). It seems reasonable to assume a difference in the reaction of the liver to

glucose given by the intravenous route and the oral route, respectively, owing to a special sensitivity to the concentration of the glucose in the blood in the portal region (SCOW & CORNFIELD, 1954).

i. *Renal excretion of glucose.* The loss of glucose in the urine following intravenous injection of 25 g. glucose is normally insignificant because the blood sugar level falls rapidly below the renal threshold for glucose. Several investigators have found the amount of glucose excreted in the urine after injection of 25 g. glucose to be less than 2 g. (AMATUZIO *et al.*, 1953, IKKOS & LUFT, 1957).

Neither will the amount of glucose lost with the urine generally affect the results of the test on oral administration of glucose. However, inter-individual differences in the renal threshold must be considered, which are probably of greater importance in the oral test where the blood sugar level is near the threshold level for a longer period.

*

j. *Secretion of insulin and consequent increase of factors raising the blood sugar level.* The interval between the rise in blood sugar concentration and increased insulin activity is not known with certainty. Evidence available has made it probable that the insulin promptly adjusts itself to the glucose level (ANDERSON *et al.*, 1956, METZ, 1960). It seems reasonable to expect an increased activity after a few minutes but a maximal effect not before 20–30 minutes after the initiation of hyperglycaemia. In diabetes the secretion of insulin is retarded (YALOW & BERSON, 1960).

It is not properly understood how early increased insulin activity and consequent fall of the blood sugar level initiates homeostatic processes.

The oral test, in which the glucose is taken up by the body for a longer period

and the rise in the blood sugar persists for a longer time than on rapid intravenous injection of glucose, might be more sensitive to the effect of increased insulin secretion and other endocrine factors which do not exert their full effect in association with the very transient increase in the blood sugar following intravenous administration.

*

On the basis of these comparisons it appears likely that the more physiological oral test might have advantages regarding the demonstration of potential diabetics but that the rapid intravenous test, owing to the absence of factors influencing absorption and difficult to assess, is superior for describing the effect of non-endocrine factors, and particularly of constitutional influences, on the results of the tolerance test.

APPRAISAL OF INTRAVENOUS GLUCOSE TOLERANCE TEST

In the present investigation the intravenous tolerance test was chosen with the injection of 100 cc. of 25% glucose. This technique has in recent years been widely used in routine clinical work and in experimental studies (HAMILTON & STEIN, 1942, GREVILLE, 1943, AMATUZIO *et al.*, 1953, DUNCAN, 1956 a, IKKOS & LUFT, 1957, WEST & WOOD, 1959). The results are described by *inter alia* the rate at which the blood sugar falls after the rapid initial rise. In order to determine this rate independently of the glucose level, the blood sugar values are plotted on semilogarithmic paper and then show a curve which is roughly linear and whose slope is taken as an expression of the rate of the glucose uptake by the tissues. This rate (k) can be expressed according to the general formula for a "monomolecular reaction":

$$k = \frac{2.303 (\log_{10} C_1 - \log_{10} C_2)}{t_2 - t_1}$$

where C_1 and C_2 designate the concentration of the glucose at two consecutive times t_1 and t_2 during the period the blood sugar is falling from maximum to fasting level.

It is still debatable whether the glucose concentration used for the calculation should be the concentration of the total glucose (HAMILTON & STEIN, 1942, CONARD, 1955, IKKOS & LUFT, 1957, WEST & WOOD, 1959) or the concentration of the glucose above the fasting blood sugar level (AMATUZIO *et al.*, 1953, DUNCAN, 1956 b) — in the former case k is hereinafter referred to as total index (T.i.) and in the latter as increment index (I.i.).

In an attempt to assess the usefulness of T.i. compared with I.i. a preparatory examination was made on a total of 50 in-patients of Departments of Internal Medicine and Obstetrics. The patients selected for this test had occasionally had glycosuria or had born children with a birthweight of more than 4 kg. Their ages ranged between 18 and 56 years (mean 33 years). The glucose in the capillary blood was measured according to Hagedorn-Jensen's method immediately before and 5, 10, 20, 43 and 60 minutes after injection of 25 g. of glucose intravenously. Zero time was said to be the moment the injection was begun.

The material was divided into 4 equally large groups according to the blood sugar value measured 5 minutes after the injection, which was considered the best interval for determining the maximal blood sugar level. The mean of total glucose and of glucose above fasting level was calculated for each group and these values were also plotted semilogarithmically (Fig. 8, based upon numbers given in Appendix II, Table 3). It was then obvious that

the best reproducibility of the line independently of the glucose level was obtained when the semilogarithmically plotted values of total glucose were used. There was, however, a slight deflexion of the line after 20–30 minutes, after which the blood sugar fall appeared to be somewhat slower as was also found by JENNY (1952), IKKOS & LUFT (1957), for example. This deflexion of the line is probably due to disappearance of the difference in the glucose concentration between the blood stream and other parts of the external space within which the free glucose had diffused. After this time the fall in the blood glucose concentration may be due to passage of the glucose from the external space to an intracellular phase, from where the glucose is taken up by metabolic processes.

A marked deflexion of the semilogarithmic curve for the increment values was found in the group with the lowest blood glucose level. In view of this deflexion it is hardly possible to give the increment index a simple mathematical expression independent of the glucose level and suitable for the calculation of correlation coefficients.

Total index was therefore chosen to describe the rate at which the glucose passed into the intracellular phase. Owing to the above-mentioned deflexion, in the calculation of k it was decided to ignore the first 20 minutes of the curve. It is true that the total glucose curve does not reflect a monomolecular reaction, since it does not go towards 0, but it has the advantage that within the range under consideration it is roughly linear, and the angle it subtends with the horizontal plane is largely independent of the glucose level.

Since rapid unexplained fluctuations have been observed in the blood glucose level (HANSEN, 1923, ANDERSON *et al.*, 1956) it was considered more valuable to have two points on the smoothed curve

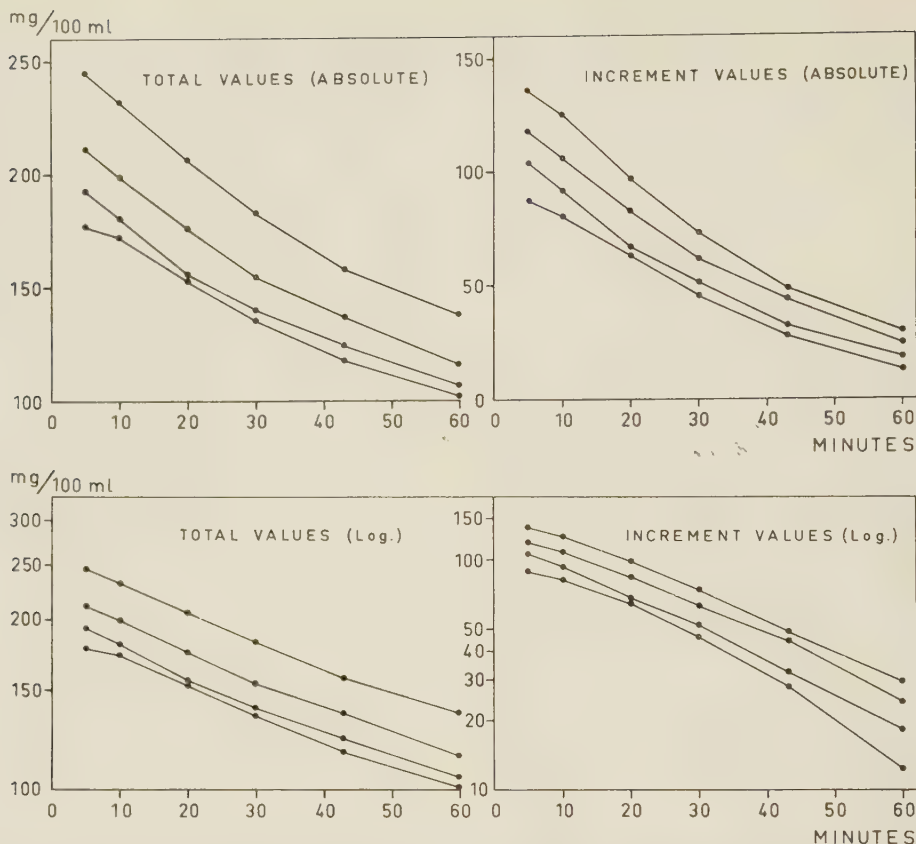


Fig. 8. Curves based upon mean values of blood sugar concentration at different intervals after injection of glucose, expressed as total and increment values, respectively, after division into quarters of the "pilot series" according to the height of the maximal glucose level.

accurately determined than a number of points with a lower degree of accuracy. Therefore several determinations were made of the glucose 20 and 43 minutes after the injection. The time of 43 minutes was chosen to simplify calculations because then the equation

$$k = \frac{2.3 (\log_{10} C_1 - \log_{10} C_2) \cdot 100}{t_2 - t_1}$$

can be shortened to

$$k = 10 (\log_{10} C_{20 \text{ min.}} - \log_{10} C_{43 \text{ min.}})$$

The T.i.-values obtained could not be used without correction for calculation of correlation coefficients. It was found that in a number of cases the blood sugar concentration during the period under consideration, *i. e.* 20–43 minutes after the injection of glucose, had fallen to such low values that one might suspect the fall to be retarded by homeostatic factors. Such a retardation would cause too low an index value. For this reason a corrected classification was constructed (see Table 28), where allowance was also made for

Table 28. Classification of total index with correction for low glucose level.

Class	Uncorrected total index	Bls ₄₃ (mg./100 ml.)	
		without steroid priming	with steroid priming
I	0—0.59		
II	0.60—0.89		
III	0.90—1.19	>130	>135
IV	1.20—1.49	125—129	130—134
V	1.50—1.79	120—124	125—129
VI	1.80—2.09	115—119	120—124
VII	2.10—	<115	<120

the blood sugar enhancing effect of steroids (see page 54). The assignment to a given class was decided by T. i. only when the blood sugar level at 43 minutes (bls₄₃) was higher than that given for the class, otherwise it was decided by bls₄₃. The correlation between bls₄₃ and T. i. proved remarkably high ($r = 0.87$).

CORRELATION BETWEEN THE GLUCOSE LEVEL AFTER INTRAVENOUS INJECTION AND THE SIZE OF THE SPACE IN WHICH GLUCOSE WAS INITIALLY DISTRIBUTED

The glucose level measured at a certain time after intravenous injection can be regarded as proportional to the size of the extracellular space in which the glucose was initially distributed. To elucidate this and to record the dependency of the increase in the blood sugar level on the ratio between different types of tissue the urine sugar values as well as the blood sugar values after 20 and 43 minutes were used. Bls₂₀ should presumably be more strongly correlated with the highest glucose level than bls₄₃. The urine sugar value may correspond to the maximal glucose increase, but its usefulness is limited by methodological inaccuracy and the varying renal threshold for glucose, which was

a probably insignificant but unknown source of error in the present investigation.

EFFECT OF GLUCOCORTICOID PRIMING ON GLUCOSE TOLERANCE TEST

Pretreatment with cortisone and cortisone-like substances has been used in recent years in association with the glucose tolerance test. Some authors have claimed that such pretreatment increases the possibility of detecting potential diabetics (for survey see CONN, 1958, FAJANS & CONN, 1961).

Recently, however, the value of the method has been questioned by WEST (1960), for example, who found such pretreatment to elevate the 2 hour value of the oral glucose test in persons whose two parents were diabetics not more than in persons without diabetes heredity. Neither did JACKSON (1961) find any definite increase in the incidence of hyperglycemic cortisone glucose tolerance tests in various types of persons in whom prediabetes might be expected, *e.g.* mothers of children overweight at birth.

In the beginning of the present investigation it was intended to use hydrocortisone provocation in the entire material largely in accordance with the method described by DUNCAN (1956 b). Thus 150

Table 29. Blood sugar levels without priming and various periods after priming with hydrocortisone or prednisolone.

	Bl _{s20}			Bl _{s43}		
	No priming			No priming		
	n	mean (mg./100 ml.)	SD	n	mean (mg./100 ml.)	SD
	145	164.5	22.1	144	128.2	24.2
Interval after priming (hours)	150 mg. hydro- cortisone		10 mg. predni- solone	150 mg. hydro- cortisone		10 mg. predni- solone
	n	mean (mg./100 ml.)	n mean (mg./100 ml.)	n	mean (mg./100 ml.)	n mean (mg./100 ml.)
2 —2 ½	1	154		1	111	
2 ½—3	2	144	6 164	2	125	6 118
3 —3 ½	12	165	6 153	12	125	6 121
3 ½—4	7	186	6 190	7	153	6 151
4 —4 ½	9	170	6 167	9	140	6 140
4 ½—5	2	181		2	139	
5 —5 ½	1	184		1	164	

mg. hydrocortisone* was given 2–4 hours before the beginning of the glucose tolerance test. The value of the method, however, proved questionable, and it was abandoned after 34 tests. In a later group of 24 persons 10 mg. prednisolone was given 2–4 hours before the glucose injection. In the selection of the latter less electrolyte-active preparation consideration was given to the possibility that the dose of hydrocortisone might have increased the size of the extracellular space during the first few hours after the injection and before the glucose increasing effect had started with the result that remarkably low blood sugar levels were obtained during the first 2–3 hours after the administration of hydrocortisone. Prednisolone, however, had largely the same effect as hydrocortisone but the smaller dose of steroid caused, as expected, a somewhat smaller increase in the blood sugar level.

The time of the maximal effect of ste-

roids after oral administration was studied by determining the average glucose level at different intervals after the administration of steroids. This level was calculated as a mean of the glucose values noted 20 and 43 minutes, respectively, after the glucose had been administered.

It is clear from Table 29 that full effect of the steroid on the blood sugar was probably not obtained until 3 ½ to 4 hours after administration. This interval agrees well with the curves of THORN, RENOLD & WINEGRAD (1957) and also with the maximum eosinophil depressive effect of these substances (WEST, 1958).

The investigation would not allow of any conclusions as to WEST's (1959) statement that glucocorticoid priming causes the blood sugar to rise further until 4–6 hours after the administration of hormone.

METHODS

MEASUREMENT OF GLUCOSE IN BLOOD

The glucose-concentration in blood was determined according to Hagedorn–Jensen

* Steroid-preparations courteously supplied by Ferring AB, Malmö.

(HAGEDORN, HALSTRÖM & NORMAN-JENSEN, 1935), on capillary blood from the finger tips.

The determination was made 4–8 hours after sampling. To prevent glycolysis sodium fluoride was added to the samples.

Each day double determinations were made on blanks containing only precipitating solution, as well as double titrations of the thiosulphate solution used against an exactly 0.05 N iodide solution.

The order of the error of titration could be judged from the mean difference between the two determinations on the thiosulphate solution. The difference was equivalent to 1.7 mg./100 ml. of glucose. On double determinations of blanks a mean difference of 3.3 mg./100 ml. was obtained, which was considered to be an expression of the total range of variation of laboratory methods.

On the first two examination days two capillary samples were collected, one of 0.1 and one of 0.05 cc., but the latter amount proved less suitable for the relatively low glucose values found. Therefore later, 4 samples of 0.10 cc. each were collected at every interval. The 4 samples were collected within a period of 2–3 minutes. In the calculation of the mean, the 3 values that were closest together were chosen in order to avoid the effect of strongly deviating values — in addition, for technical reasons, it was sometimes possible to obtain only 3 samples in the short time available for sampling. The values excluded deviated largely equally on both sides of the mean range.

In order to estimate the total error of the determination of the glucose level, the arithmetic mean was calculated of the 3 most similar values for each person and sampling time, and then the mean of the deviations of the single observations from this arithmetic mean was calculated. The

mean of these deviations, 3.1 mg./100 ml., was 14% of SD of the blood sugar values calculated for the whole material. The corresponding figures for all 4 values were 4.1 mg./100 ml. and 17% of SD, respectively.

The samples were collected in 2–3 minutes. During these minutes the blood sugar fell. The size of the fall is indicated by the mean value after 20 minutes, for the first sample it was 166.1 mg./100 ml. while for the fourth sample it was 164.2 mg./100 ml. The corresponding values at 43 minutes were 132.0 and 130.0 mg./100 ml.

To avoid thrombophlebitis the patients received 10,000 I. U. heparin* together with the glucose, which has been shown not to affect the glucose values (DUNCAN, 1956 a).

MEASUREMENT OF GLUCOSE IN URINE

The urine produced from immediately before the injection of glucose until 60 minutes afterwards was collected in one portion. It was examined by one and the same person with Tes-Tape "Lilly".** To check the reliability of these determinations the glucose in specimens from 35 consecutive samples was measured also polarimetrically (HAMMARSTEN, 1955). The results are demonstrated in Fig. 9.

RESULTS

To describe the results of glucose tolerance test in groups with varying risk of being a diabetes gene carrier, cumulative frequency diagrams were constructed for the distribution of total index and blood sugar concentration (Fig. 10). The

* Courteously supplied by Vitrum, Stockholm.

** Courteously supplied by Lilly and Co.

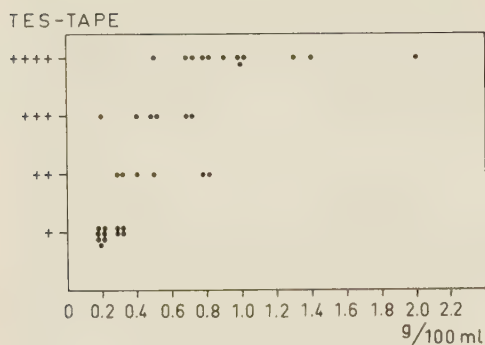


Fig. 9. Comparison between Tes-Tape scores and urine sugar concentration as measured by polarimetric method.

figures on which these diagrams are based are given in Appendix II, Table 4.

The correlations between the results of the intravenous tolerance test and different somatic determinations are expressed as correlation coefficients (Table 30).

EFFECT OF NOT STRICTLY COMPARABLE STUDY-GROUPS ON THE RESULTS OBTAINED

Two of the subjects showed signs of shock during the intravenous test, which was therefore discontinued. In one case the psychic reaction was so intense that the test could not be performed. Two of the subjects had by mistake eaten breakfast on the morning of the examination so that the test could not be performed. In one case the blood sample obtained after 43 minutes was lost.

In the calculation of the correlations the glucose values from the entire material were used, besides which the values were divided into 3 subgroups, namely:

1. Values for which there was no reason to doubt their correctness (103 probands).
2. Values after glucocorticoid priming (58 probands).

3. Values from examination in which only 90 cc glucose-solution was given (11 probands), as well as cases in which the injection was retarded owing to ruptured vessels (14 probands) and finally values from 2 examination days (16 probands) during which the mean glucose value was remarkably different from the mean of the entire material which could later be explained by subsequent analysis of the composition of the groups examined on these days.

As to the 3 subgroups $bl_{s_{43}}$ was used for the comparisons. No substantial differences were found between the types of correlation coefficients obtained (Table 30).

DISCUSSION

GLUCOSE TOLERANCE IN ASSUMED CARRIERS OF THE DIABETES GENE

No correlation was found between the results of the glucose tolerance test independently of the method used for estimating, and the risk of being a carrier of the diabetes gene. This is in disagreement with the findings of most earlier investigators (PINCUS & WHITE, 1934, WHITE, 1955, CONN, 1958) though it should be observed that some evidence questioning the value of the glucose tolerance test for detecting prediabetic conditions is also available (UNGER, 1957, LAMBERT, JOHNSON & PAUL, 1961, KLIMT *et al.*, 1961), and with special reference to youths, MACKLER & FISCHER (1934) found no constant pathologic curves on an oral tolerance test among 30 sibs, aged 2–19 years, of juvenile diabetics. The observation might thus be explained by the low age of the subjects examined. It is well-known that the glucose tolerance decreases with increasing age (CHESROW & BLEYER, 1954, SILVERSTONE *et al.*, 1957) and the tolerance test may then be more applicable for tracing a prediabetic state.

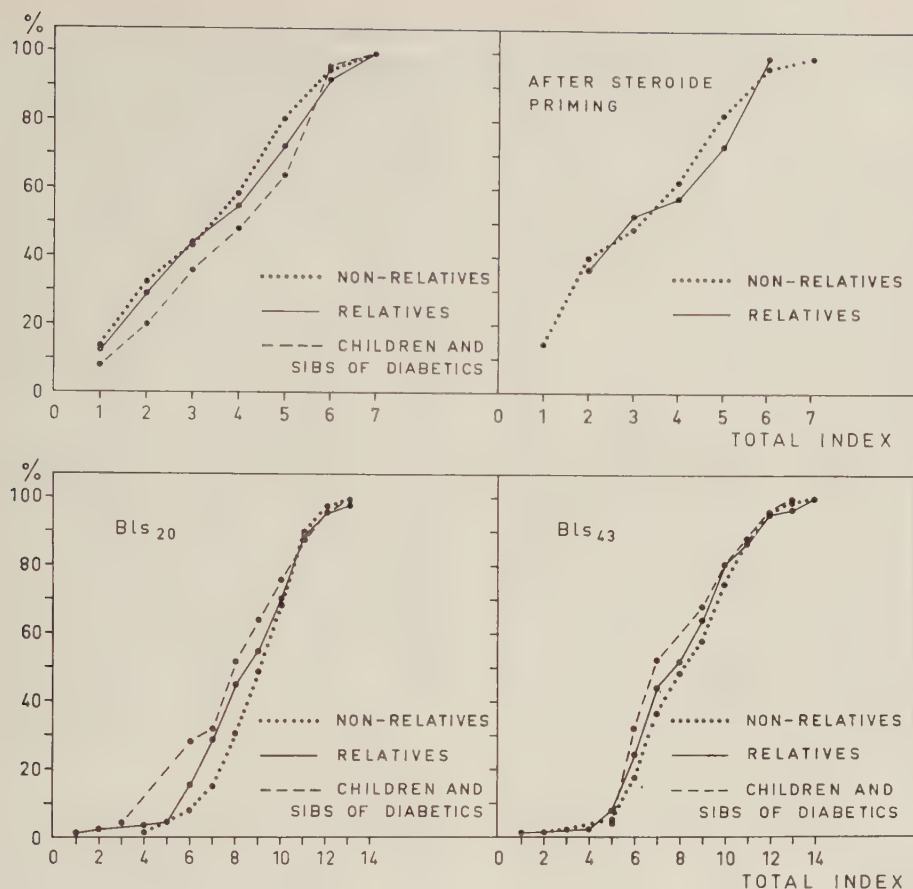


Fig. 10. Cumulative diagrams of distribution of total index, and blood sugar concentration 20 and 43 minutes after glucose injection, among relatives and non-relatives of diabetics.

Neither can it be excluded that the method used with its unphysiological administration of glucose is not so good as the oral test for detecting prediabetic conditions. In this respect the longer period during which glucose is taken up on oral administration might be important. On intravenous administration with rapid injection of glucose the hyperglycaemic phase is so short that the endocrine mechanisms regulating the blood sugar concentration may not have time to react fully.

*

The investigation underlines that minor deviations in the results of the glucose tolerance test allow of no conclusions as to whether a person will develop diabetes or not. When the results of the tolerance test are correlated with the risk of being a carrier of the diabetes gene it might be possible roughly to estimate the risk of diabetes development, but even then the considerable intra-individual variations of the results of the glucose tolerance test must be considered, as pointed out by FREEMAN *et al.* (1942) and others. It can-

Table 30. Coefficients of correlation between results of glucose tolerance test and various somatic data (For evaluation of significance, See Appendix V).

		Bls ₂₀	Bls ₄₃	Bls ₄₃ x ₁	Bls ₄₃ x ₂	Bls ₄₃ x ₃	Urine-sugar	Total index
	n	203	202	103	58	41	190	202
Bls ₂₀	203							
Bls ₄₃	202	0.79						
Bls ₄₃ x ₁	103	0.74						
Urine-sugar	190	0.18	0.13	0.05				
Total index	202	—0.52	—0.87	—0.86	—0.84	—0.87	—0.06	
Weight	467	—0.34	—0.21	—0.13	—0.18	—0.42	—0.36	0.08
Fat-free weight	208	—0.31	—0.22	—0.21	—0.29	—0.22	—0.31	0.07
Height	467	—0.28	—0.20	—0.14	—0.36	—0.24	—0.27	0.07
Circumf. chest	146	—0.39	—0.25	—0.26	—0.12	—0.48	—0.26	0.12
Tibia length	208	—0.24	—0.14	—0.10	—0.27	—0.19	—0.32	0.03
Radius length	208	—0.25	—0.13	—0.15	—0.13	—0.13	—0.33	—0.02
Condyl. breadth	208	—0.30	—0.25	—0.16	—0.25	—0.43	—0.33	0.14
Bistyl. breadth	208	—0.22	—0.16	—0.25	—0.07	—0.05	—0.25	0.06
Handgrip	208	—0.17	—0.16	—0.20	—0.12	—0.15	—0.18	0.12
Shoulder thrust	206	—0.13	—0.11	—0.11	+0.02	—0.23	—0.09	0.08
Shoulder pull	206	—0.12	—0.13	—0.19	—0.01	—0.14	—0.16	0.15
Skinfold back	208	—0.09	—0.11	—0.08	—0.04	—0.16	0.00	0.12
Skinfold lat. chest	208	—0.09	—0.11	0.00	—0.01	—0.27	—0.04	0.10
Skinfold abdomen	208	—0.12	—0.11	—0.06	—0.01	—0.23	—0.03	0.12
Weight minus fat-free weight	208	—0.07	0.01	0.07	0.13	—0.22	—0.09	—0.01

¹ Refers to subgroups given on page 56.

not be excluded that the group with extreme values for the tolerance test contains a larger number of carriers of the diabetes gene that will later develop the disease, which would then suggest that the glucose tolerance test reflects factors increasing the penetrance of the disease.

Treatment 2–4 hours before the glucose tolerance test with 150 mg. hydrocortisone or 10 mg. prednisolone was not found to increase the value of the test for diagnosing prediabetic conditions.

DEPENDENCE OF THE INTRAVENOUS GLUCOSE TOLERANCE TEST ON BODY VOLUME AND BODY BUILD

On rapid intravenous injection of glucose the blood sugar level appears to be initially dependent on the ratio between the amount of glucose injected and the volume of fluid in which it is rapidly dis-

tributed. Gradually, however, the blood sugar level is also influenced by the slower passage of glucose from this external space, which may be largely identical with the extracellular space (FRANCKSON, CONARD & BASTENIE, 1959), to the intracellular compartments. Whether this passage depends upon a pressure gradient from one phase to another or there exists a special transport system for glucose through the cell membrane (PARK *et al.*, 1959) is not known with certainty — it is probably a result of both factors being of different importance in different tissues.

The values considered dependent on the size of the external space, namely the blood sugar levels at 20 and 43 minutes after injection of glucose and the amount of urinary sugar, are negatively correlated with bodyweight, (table 30). On comparison

between the significance of the different somatologic radicals certain differences were found. The strongest correlation was found between blood sugar levels and length-factor and sturdiness-factor, respectively. The correlation between the glucose level and muscle-factor was lower throughout — possibly it was only indirect and might be explained by the strong positive correlation between muscle-factor and sturdiness-factor. It must, however, be borne in mind that estimation of muscle volume by dynamometric recordings is probably much less accurate than measurement of length-factor and sturdiness-factor.

No significant correlation was found between the glucose level and body fat.

In the evaluation of these correlations it should be remembered that the correlation between bodyweight on one hand and length-, sturdiness-, muscle- and fat-factors on the other were of the same order (Appendix III, Table 1).

The observation that the fluid space in which the glucose rapidly diffuses was correlated best with the fat-free volume can probably be explained by the relative decrease of the extracellular space found in obesity (LJUNGGREN, IKKOS & LUFT, 1957, POSBORG-PETERSEN, 1957). It has also been suggested (LICHTFIELD, 1959) that the hypertonicity of the extracellular fluid in hyperglycæmia is of significance. If that is the case one may imagine an increased transfer of intracellular fluid from the muscle cells than from the fat cells with the much smaller fluid phase of the latter.

The total index, at least if calculated as here on the fall in the glucose concentration occurring after the first 20 minutes, is due, above all, to the passage of the glucose from the external compartments to the intracellular space, where it is used up by metabolic processes. Since no signi-

ficant correlations were found between total index and the somatologic radicals, the rate of this passage appears not to be dependent on the ratios between the different types of tissues. In the evaluation of these correlations it should be borne in mind that total index might also be dependent on factors not measured, such as glucose uptake by the liver, and tending to mask any variation of total index with body build. Further, if the transport of the glucose through the cell wall is not owing chiefly to a glucose gradient across the cell membrane it might be less dependent on the ratios between the different types of tissue and the distribution of fluid.

In the assessment of the significance of the results obtained it should perhaps be recollected that the effect of the fat is said to depend on whether the latter is growing or stationary (BEAUDOIN *et al.*, 1953). In view of the age of the persons studied in the present investigation it may be assumed that the fat was on the increase and should thereby tend to depress the level of the glucose tolerance curve.

The findings described above suggest that the dose of glucose used should be adjusted according to fat-free bodyweight if the result is to warrant any conclusions on the height of the sugar curve. The same opinion is expressed by WIERZUCHOWSKI (1958), WEST & WOOD (1959), and others. The formulae used for the calculation of fat-free weight are, however, less satisfactory and this is probably the main reason why the correlation between bls_{20} and total weight was numerically stronger than that between bls_{20} and fat-free weight. It may therefore be advantageous to adjust the dose according to total body weight except for very obese persons, for whom it might be better to estimate the fat-free weight.

IX DISCUSSION

OCCURRENCE AND PENETRANCE OF THE DIABETES GENE

The present investigation emphasized the conception of the hereditary nature of diabetes mellitus. The values observed fit in best with an autosomal recessive inheritance, though the results of the analysis are also to a certain degree compatible with a dominant gene of low penetrance. The material does not lend itself well to evaluation of the possibility of aberrant, numerically less important types of diabetes. As to the diabetes gene, however, there appears to be no distinction between diabetes of chiefly juvenile and diabetes of chiefly adult onset. The asthenic features ascribed to young diabetics are referable to the effect of the disease during childhood and adolescence.

Broadly speaking, assuming autosomal recessive inheritance, manifestation occurs chiefly among homozygotes and then in only about 80 %. In this respect, however, the sexes differ in that the morbidity among elderly persons is higher in females than in males.

*

Under certain conditions heterozygotes may also develop the disease, and this may then help to explain a certain overmorbidity among groups in which the frequency of diabetes is definitely higher than the 4 % expected with a gene frequency of 0.2 and manifestation in homozygotes only.

As an example of such groups, reference might be made to acromegals in whom

frank diabetes is said to occur with a frequency of about 25 % (For survey see MILLER, 1960). The diabetes in acromegaly can probably be explained by the assumption that the increase in growth hormone unduly stresses the beta-cells, which successively become exhausted and which have been shown to develop degenerative and atrophic changes in different types of animals (For survey see YOUNG & KORNER, 1960).

It seems probable that also other blood-sugar enhancing factors, *e.g.* cortisone, administered, or produced in increased amount indirectly stimulate the beta cells to an increased production of insulin, which may result in an undue stress on the insulin producing apparatus.

A stress of endocrine origin might be of significance in the causation of the increased frequency of diabetes among women with many children and possibly also among women who have several abortions.

*

If the insulin antagonistic activity becomes sufficiently intense, even persons without the diabetes gene might develop diabetes, particularly if the function of the pancreas is impaired by some inflammatory or vascular lesion, for example. But it seems reasonable to suppose that this risk of developing diabetes is greater even if the diabetes gene occurs only in a single dose. Only when the gene occurs in a double dose, however, will an insulin antagonistic activity within the normal biologic

range cause the penetrance of the genotype.

In the absence of pronounced pathological conditions, factors favouring penetrance seem to be obesity and as far as women are concerned reproduction. But it cannot be concluded that this relationship is causal and it cannot be excluded that social environments or endocrine influences may contribute to the correlations.

RELATION BETWEEN CONSTITUTION AND PENETRANCE OF THE DIABETES GENE

The investigation showed that a certain tendency to overweight at the 18 year level occurs before the manifestation of diabetes in young males. This overweight may be related to the early sexual development of prediabetic children. As pointed out by several investigators (for survey see TANNER, 1955) early maturers are not only persons whose growth is advanced at all ages. Also as adults they have more weight for height than late maturers. Children and youths who develop diabetes appear to fit in well with this picture.

A close correlation exists between the rate of sexual maturation and growth. Thus, the chief signs of sexual maturation, *i. e.* menarche in the female and corresponding genital development in the male, is generally preceded by accelerated linear growth, the increase being greatest 0.5 to 1.5 years before these occurrences, *i. e.* at 11 years in girls and 13 years in boys (For survey see TANNER, 1955). This period of increased endocrine activity is accompanied by a higher frequency of the diagnosis of diabetes with a peak frequency some 2 years earlier in girls than in boys, *i. e.* coinciding largely with the period of accelerated linear growth in both sexes, which has been pointed out by SECKEL (1960) and others.

Though psychological factors may be of significance in the explanation of the connection between puberty and the increased frequency of manifest diabetes, a possible diabetogenic effect of various growth promoting factors active in puberty must be considered. The most important of such factors seem to be the pituitary growth hormone and various androgenic agents. While some authors claim that the steroid growth factor is the chief initiator of acceleration of skeletal growth at puberty (KINSELL, 1954), others propound that the pituitary growth hormone is of greater importance in respect to linear growth (SECKEL, 1960).

An increase in the production of 11-oxy-steroids with their well known diabetogenic effect is probably of less importance since its protein catabolic effect does not appear to agree with the observed increase in skeletal and muscular growth. The possibility must, however, be emphasized that though the acceleration of growth and the increased penetrance are parallel, they are not necessarily of uniform origin.

Summarizing, a common endocrine background of juvenile diabetes cannot be concluded with certainty, but the hypophyseal growth hormone and possibly androgenic substances are probably of importance. It seems reasonable to assume that these hormones also in the following decades favour penetrance, and explain the increased frequency of the disease in males up to the age of 50 years. This sex difference, however, may also to some extent be due to the possibility that endocrine factors in females of fertile age tend to counteract penetrance of the disease and thereby prevent its development until the menopause.

In animal experiments the diabetogenic effect of the pituitary growth hormone seems to be well documented (HOUSSAY & BIASOTTI, 1931; HOUSSAY & ANDERSON,

1949; YOUNG, 1937; COTES, REID & YOUNG, 1949), and in human diabetics increased values for the growth-hormone have been found (FORSMAN & GEMZELL, 1960; EHR- LICH & RANDLE, 1961).

CAUSE OF RETARDATION OF GROWTH IN JUVENILE DIABETES

An increasing number of juvenile diabetics have a clinical picture of total diabetes with cessation of insulin production within the first few years of the disease (WRENSHALL, 1960), and a corresponding increase in the requirements for exogenous insulin and difficulty in control of the disease. According to WHITE (1960), by the fifth year 90 % of diabetic children show such a totally diabetic state.

This has been confirmed by histological findings made in the pancreas of diabetics aged 1–29 years (MACLEAN & OGILVIE, 1959) that in those in whom the disease had run an acute course with death supervening within a matter of a few weeks, the average size of the islets was greater than in a group of control subjects. In contrast, the pancreata from those patients with a more chronic disease course contained islets significantly smaller than in the controls.

The retardation of growth seems to be more pronounced if the disease becomes manifest before the period of rapid growth — about the age of 13 years in boys —, and may be due to lack of production of insulin with consequent reduction of the effect of pituitary growth hormone or possibly testosterone on the puberal growth spurt.

It appears that both these hormones require the presence of insulin to exert their anabolic effect. In animal experiments growth hormone has been shown to lack anabolic effect in the absence of insulin

(MILMAN, de MOOR & LUKENS, 1951; SCOW & CHERNICK, 1960). Testosterone has been shown to have no depressing effect on nitrogen excretion in pancreatectomized female dogs (SIREK & BEST, 1953).

The present state of our knowledge will not allow of any discussion of the possibility that the lack of insulin *per se* might contribute to the retardation of growth. Insulin has, however, been shown to have an N-retaining effect also in hypophysectomised animals (SALTER & BEST, 1953, LUKENS, 1958).

Evidence is available for the assumption of reduced androgen production after the young male had diabetes for some years (BERGQUIST, 1954 b) with consequent impairment of sexual as well as muscular development. In the treatment of diabetic dwarfism testosterone seems to be most effective (WHITE, 1959).

The retardation might also occasionally be ascribed to dietary restrictions during the years of growth.

CAUSE OF OVERWEIGHT OF NEWBORNS OF FUTURE DIABETICS

Inherited growth factors might be the cause of the tendency to overweight at birth of children of women as well as men who later in life become diabetic. Since the birth of several children appears to favour penetrance considerably, the more marked increase when the mother develops diabetes can be explained partly by the overweight, at birth, of children of high birth number.

RELATION BETWEEN GLUCOSE TOLERANCE CURVE AND RISK OF DEVELOPING DIABETES

The result of the glucose tolerance test may be regarded largely as reflecting a certain endocrine situation. It may be

assumed that the curve is often elevated by diabetogenic factors, but that in conditions with a strong secondary production of insulin, the curve is even depressed as long as the beta-cells are intact. If hyperactivity is followed by a state of exhaustion, the glucose tolerance curve may be pathologically elevated during a period before the appearance of manifest diabetes. This period may be longer among elderly people.

Concerning young males, the result of the intravenous glucose tolerance test with

and without glucocorticoid priming did not appear to be related to the risk of being a carrier of the diabetes gene. However, it cannot be excluded that the group with the highest glucose curves includes an increased number of such gene carriers who will develop diabetes, which would confirm that the glucose tolerance curve reflects factors increasing penetrance. This can only be proved by a longitudinal study, which is being planned.

SUMMARY

Attempts were made to trace all male diabetics between the ages of 17 and 25 years in a well defined geographical area and all 18 year old male relatives of diabetics in that area.

The probands and age-matched controls were studied from various angles in order to obtain data to elucidate various genetical and constitutional aspects of diabetes mellitus.

The following observations were made:

GENETIC-STATISTICAL ANALYSIS

- a. Diabetes occurred with increased frequency among relatives of juvenile diabetics and the distribution of the disease was compatible with the assumption of a uniform diabetic gene.
- b. An autosomal recessive mode of inheritance seemed to be the most likely transmission of diabetes mellitus. Then the mutant allele would occur at about 30 % of the general population of the investigated area. Penetrance would occur during lifetime in about 70 % of male and 90 % female homozygotes. If penetrance occurs among heterozygotes it appears to be low.
- c. Dominant inheritance seemed to be less likely but could not be excluded. The proportion of pathogenic alleles can then be calculated to be of the order of 0.05 with penetrance among about

25 % in male and 30 % in female gene carriers.

- d. The possibility of different genotypes manifesting the same or similar clinical picture could not be excluded but appeared less likely. If a main genotype be assumed the occurrence of aberrant genotypes with similar manifestations of the disease must be low.

GROWTH AND DEVELOPMENT OF DIABETICS AND ASSUMED CARRIERS OF THE DIABETES GENE

- a. Children and sibs of diabetics at 13, about 18 and about 50 years of age tended to be taller and heavier than the controls.
- b. Attempted somatologic differentiation regarding the cause of overweight at 18 years of children and sibs of diabetics suggested an increase not only of height but also of skeletal sturdiness and fat-free weight.
- c. 18 years old males who developed diabetes within the following 5 years tended to be heavy for height. The lack of strictly comparable controls prevented satisfactory somatologic differentiation — though certain evidence was available for the assumption of increased skeletal sturdiness and muscular strength.

- d. Among males who developed the disease before 13 years, at 18 years a certain reduction in weight, height and skeletal sturdiness as well as muscle strength was noted. It could not be decided whether growth was inhibited in males who developed the disease between 13 and 18 years.
- e. The amount of subcutaneous fat in juvenile diabetics tended to increase with the duration of the disease.
- f. At 50 years of age the diabetic was overweight independent of the duration of the disease.

BIRTHWEIGHT OF DIABETICS AND ASSUMED CARRIERS OF THE DIABETES GENE

- a. Female diabetics at the 50 year level and 70 year level had 1–2 children more than male diabetics and non-diabetic women of corresponding ages.
- b. Children of prediabetic mothers had a birthweight of on the average 400 g. more than normal. A corresponding increase of about 150 g. was observed when the father was found to develop diabetes, and an increase of about 100 g. when the proband himself had developed diabetes before the age of 25 years. An increase of about 100 g. was also found for the sibs of the young diabetic probands.
- c. Overweight of the proband at birth when the mother later developed diabetes may be ascribed partly to an increase of weight with increasing birth number. This increase in weight was calculated to be about 100 g.
- d. A certain overweight when the mother developed diabetes might also be ascribable to the mother's overweight which was found to be correlated with the birthweight of her children.

INTELLECTUAL ENDOWMENTS OF YOUNG DIABETICS AND ASSUMED CARRIERS OF THE DIABETES GENE

- a. The intelligence of juvenile diabetics was found to be somewhat, but not significantly, higher than normal and did not differ with the duration of the disease.
- b. No such higher degree of intelligence was found among relatives of the diabetics.
- c. Diabetics was found more often in the higher socio-economic classes.

INTRAVENOUS GLUCOSE TOLERANCE TEST

A glucose tolerance test was performed by rapid intravenous injection of 100 cc of 25 % glucose solution. The results were judged by the rate at which the glucose level in the blood fell, expressed as total glucose concentration during the period 20–43 minutes after the injection of the glucose: this rate was called total index.

The following observations were made:

- a. Total index did not appear to be related to an increased risk of developing diabetes, as judged from genetic calculations.
- b. Total index did not appear to be correlated with certainty with different somatic measurements.
- c. Administration of hydrocortisone or prednisolone 2–4 hours before the injection of glucose appeared to raise the level of blood-glucose but not to affect the ratios between the distribution of total index among relatives of diabetics compared with non-relatives.
- d. The height of the blood glucose curve after intravenous injection of glucose did not seem to be related to the increased risk of developing diabetes owing to relationship with a diabetic.

- e. The level of the blood glucose curve appeared to be dependent mainly on the relative volume of fat free tissue of the subject tested.

*

The investigation added evidence for the inheritability of diabetes mellitus. The disease appears to be caused by a uniform mutant gene with a frequency of 0.17 to

0.20 in the population studied and then develops mainly in homozygotes. In these the frequency of manifestation increases with age, but does not become 100 %. Increased growth and, as far as women are concerned, increasing number of pregnancies favour manifestation. In 20 year old male carriers of the diabetes gene, the glucose tolerance, as judged by rapid intravenous injection of 25 g. glucose is not decreased.

ACKNOWLEDGEMENTS

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*

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APPENDICES

I—V

Appendix I.

Table 1. Weight and height at induction in series B (subgroups I—VI described on page 9).

		Examined by Author	Not examined by Author					Total	VI
			I	II	III	IV	V		
B	n	209	154	44	32	18	10	467	8
	weight	64.4	63.6	64.7	65.9	62.2	62.5	64.3	
	SD	7.5						SD 7.5	
	height	175.5	176.2	175.4	176.5	174.3	172.9	175.6	
	SD	6.5						SD 6.5	
Br	n	106	78	23	16	8	6	237	
	weight	64.5	63.7	65.0	68.3	63.7	62.8	64.5	
	height	175.8	176.4	176.2	181.3	175.4	173.3	176.3	
Bc	n	103	76	21	16	10	4	230	8
	weight	64.2	63.5	64.4	63.6	61.5	62.3	64.0	
	height	174.9	176.0	174.5	171.7	173.7	172.3	174.9	

Appendix I.

Table 2. Distribution of occupations, Series B.

Occupation	Series Br				Series Bc		Total B	
	Diabetes in parents or sibs	Examined by Author	Not examined by Author	Total Br	Examined by Author	Not examined by Author		Total Bc
Total	n	53	106 64.5 176.0	131 64.6 176.6	237 ¹ 64.5 176.3	103 64.2 174.6	230 64.0 174.9	467 64.3 175.6
Agriculture		6 (13.2 %)	21 64.4 174.8	16 65.8 176.7	37 (15.5 %) 65.0 175.6	17 63.5 173.0	14 63.1 174.0	68 64.2 174.6
Industry		10 (18.9 %)	24 64.6 175.8	26 64.0 174.8	50 (21.0 %) 64.3 175.3	39 64.7 174.9	38 60.3 172.9	127 62.9 174.5
Commerce		7 (13.2 %)	15 65.2 176.8	15 60.4 176.1	30 (12.6 %) 62.8 176.5	15 61.6 175.7	16 61.6 174.8	61 62.2 175.8
Miscellaneous		12 (22.6 %)	18 63.1 173.9	24 61.8 174.5	42 (17.4 %) 62.1 174.2	17 63.9 173.9	12 63.9 173.9	71 62.9 174.1
Handicraft		6 (11.3 %)	10 59.6 176.6	9 66.3 178.2	19 (8.0 %) 62.8 177.4	9 67.0 175.0	14 63.6 174.6	42 64.0 176.0
Student		12 (22.6 %)	18 67.8 178.5	41 67.5 178.8	59 (25.2 %) 67.6 178.7	6 66.8 176.5	33 66.3 178.2	98 67.1 178.4

¹ If Br is corrected to match Bc, weight will be 64.4 kg. and height 176.2 kg.

Appendix I

Table 3. Distribution of occupations of fathers, Series A and B.

Father's occupation	Series	A			Br	Bc
		6th reg. distr.	7th reg. distr.	Total		
Agriculture		17 28.3 %	7 14.5 %	24 22.0 %	25 23.6 %	20 19.4 %
Farm labourers		2 3.3 %	3 6.1 %	5 4.6 %	3 2.8 %	5 4.9 %
Industry workers		12 20 %	11 22.4 %	23 21.1 %	27 25.5 %	32 31.1 %
Salaried employees, foremen		7 11.7 %	8 16.3 %	15 13.8 %	15 14.2 %	12 11.7 %
Unskilled labourers		12 20 %	6 12.2 %	18 16.5 %	5 4.7 %	4 3.9 %
Commerce		2 3.3 %	5 10.2 %	7 6.4 %	8 7.5 %	5 4.9 %
Professional employees		5 8.3 %	2 4.1 %	7 6.4 %	12 11.3 %	3 2.9 %
Employers		3 5 %	4 8.2 %	7 6.4 %	9 8.5 %	12 11.7 %
Not known		0	3 3.6 %	3 2.8 %	2 1.9 %	10 9.7 %

Appendix I

Table 4. Distributions and meanweights of parents of probands in series B according to their socio-economic level. (Division into social groups described page 17.)

Sex	Social group	Series Br		Series Bc	Weight series B mean (kg)
		Diabetes known in			
		Parent or sib	Grandparent, uncle, aunt or cousin		
Female	I	1 (5 %)	8 (10 %)	4 (4 %)	62.5
	II	5 (23 %)	32 (38 %)	20 (21 %)	68.1
	III	16 (73 %)	44 (52 %)	72 (75 %)	68.6
Male	I	1 (5 %)	8 (10 %)	4 (4 %)	77.3
	II	6 (23 %)	30 (38 %)	19 (21 %)	79.9
	III	15 (73 %)	42 (52 %)	69 (75 %)	76.9

Appendix II
Table 1. Characteristics of series B

		n	Mean-value	SD	Unit	Class-breadth	Lowest class-breadth
1	Weight at 13	114	43.7	6.8	kg	3.0	31.0—33.9
2	Height at 13	114	155.1	8.1	cm	3	138—140
3	Weight at induction	467	64.3	7.5	kg	3.0	45.0—47.9
4	Height at induction	467	175.6	6.5	cm	3	158—160
5	Tibia length	208	39.0	2.8	"	1.0	32.0—32.9
6	Radius length	208	25.8	1.4	"	0.5	21.0—21.4
7	Condylar breadth	208	9.56	0.42	"	0.2	8.3—8.4
8	Bistyloid breadth	208	5.82	0.30	"	0.1	5.0
9	Circumf. chest	146	90.2	5.3	"	2	74—75
10	Shoe-size	204	42.1 ¹	1.5 ²	Sw. size	1	37
11	Handgrip	208	41.1	5.8	kilopond	2	27—28
12	Shoulder thrust	206	55.9	11.8	"	3	29—31
13	Shoulder pull	206	34.1	6.8	"	2	20—21
14	Skinfold back	208	6.7	1.2	mm	1	3
15	Skinfold lat. chest	208	5.1	2.1	"	1	3
16	Skinfold abdomen	208	6.0	2.3	"	2	3—4
17	Weight min. fat-free weight	208	11.6	9.1	% of weight	2	-8 — -7
18	Fat-free weight	208	59.1	5.8	kg	2	44—45
19	Hair-growth chest	208	2.2	1.3	See LINDEGÅRD (1956)		1
20	Blood-pressure systolic	208	126	11	mm Hg	5	95—99
21	Blood-pressure diastolic	208	81	6	"	5	50—54
22	Pulse-rate	131	67.1	10.0	beat/min	3	46—48
23	Birthweight	369	3.54	0.57	kg	0.25	2.00—2.25
24	Birthlength	249	51.2	2.2	cm	1	46
25	Sibs' birthweight	229	3.57	0.47	kg	0.25	2.00—2.25
26	Mother's weight	376	68.9	14.7	"	3.0	45.0—47.9
27	Mother's height	374	164.2	5.3	cm	3	152—154
28	Father's weight	345	78.6	9.6	kg	3.0	51.0—53.9
29	Father's height	352	175.0	6.2	cm	3	155—157
30	Mother's age at 1st menstr.	356	13.8	1.3	year	1	10
31	Mother's age at 1st partur.	374	25.3	4.7	"	1	17
32	Number of father's sibs	374	4.6	2.0	number	1	0
33	pat. cousins	359	4.0	1.8		= number of class	0
34	mother's sibs	384	4.5	2.1	"	1	0
35	mat. cousins	365	3.8	1.8		= number of class	0
36	sibs	398	2.4	1.7	"	1	0
37	Mean score intel. test	465	4.49	1.75	see page	15	1
38	Manual labour	207	2.1	0.7	"	17	1
39	Intellectual work	207	1.7	0.6	"	"	1
40	School-education	412	1.5	0.7	"	"	1
41	Socio-economic level	202	2.5	0.6	"	"	1
42	Urbanization	203	1.9	0.9	"	"	1
43	Days after enlistment	208	21.8	14.0	day	2	0—1
44	Bls ₂₀	203	164.5	22.1	mg./100 ml.	10	80—89
45	Bls ₄₃	202	128.2	24.2	"	10	50—59
46	Bls ₄₃₁	103	127.7	21.4	"	10	50—59
47	Bls ₄₃₂	58	132.7	22.0	"	10	50—59
48	Bls ₄₃₃	41	122.5	29.6	"	10	50—59
49	Urine sugar	190	2.6	1.2	Tes-Tapescore		1+
50	Total index without correction	202	3.4	1.7		0.25	0.35—0.59
51	Total index corrected	202	3.9	1.9		See table 28	

¹ = 28 cm. or English size 8² = English size 1.2

Appendix II

Table 2.

Age in years	Penetrance in per cent of $P_{\max}$ for respective sex at different ages				Penetrance among males in per cent of $P_{\max}$ for females (Kristianstad)		
	Males		Females		Uncorrected for sex ratio	Corrected for sex ratio	Sex ratio 1952, Kristianstads län
	Kristianstad	Birmingham	Kristianstad	Birmingham			
4	3.2	0.8	2.8	0.4	2.5	2.3	1.05
9	6.0	2.8	4.0	1.2	4.6	4.4	1.06
14		4.7		2.7			
19	13.3	8.0	6.8	4.1	10.1	9.6	1.06
24		11.0		5.2			
29	18.9	15.0	9.2	7.1	14.4	13.7	1.03
34		19.3		9.1			
39	26.5	24.3	11.7	11.3	20.2	19.5	1.02
44		30.8		15.5			
49	37.7	40.6	19.3	22.4	28.8	28.0	1.01
54		52.5		35.0			
59	56.6	65.0	45.7	50.2	43.2	43.1	0.95
64		78.1		67.1			
69	80.3	87.6	78.8	82.4	61.3	63.2	0.90
74		94.6		92.8			
79	97.6	98.7	97.5	98.5	74.5	78.6	0.86
84		99.9	99.7				
89	100.0	100.0	100.0	100.0	76.4	80.8	0.81

Appendix II

Table 3. Mean values of blood sugar expressed as total- and increment-values respectively in the "pilot series" divided into quarters according to the highest blood sugar level (cf. Fig. 8).

Time after zero (min)	I	II	III	IV
Total glucose (mg./100 ml.)				
5	177.7	193.0	211.7	245.2
10	172.7	181.1	199.4	232.6
20	153.2	155.9	175.9	206.5
30	135.2	139.9	154.5	182.8
43	117.2	123.9	136.5	157.6
60	101.2	105.9	115.4	137.6
Increment glucose (mg./100 ml.)				
5	88.9	105.3	119.3	137.3
10	82.0	93.4	107.8	126.5
20	64.4	68.2	84.2	98.6
30	46.3	52.2	62.9	74.5
43	28.3	32.9	44.9	49.7
60	12.4	18.2	24.2	29.8

Appendix II

Table 4. Distribution of relatives and non-relatives in series B on total index, bls_{20} and bls_{43} .
(cf Fig. 10).

a = with glucocorticoid priming b = without priming c = a + b

Total-index (classes given in table 28)	Non-relatives			Relatives ¹			Children + sibs of diabetics		
	a	b	c	a	b	c	a	b	c
1	5	9	14	—	11	11	—	2	2
2	9	10	19	7	8	15	2	1	3
3	3	8	11	3	10	13	1	3	4
4	5	11	16	2	8	10	—	3	3
5	7	15	22	3	13	16	—	4	4
6	5	10	15	5	13	18	4	4	8
7	1	4	5	—	7	7	—	1	1

BlS_{20} (mg./100 ml.)	Non-relatives			Relatives ¹			Children + sibs		
	a	b	c	a	b	c	a	b	c
80—89					1	1			
90—99					1	1			
100—109							1		1
110—119		1	1		1	1			
120—129					1	1			
130—139	2	5	7	2	8	10	1	5	6
140—149	2	5	7	1	11	12		1	1
150—159	4	12	16	4	11	15	2	3	5
160—169	8	11	19	1	8	9		3	3
170—179	7	13	20	5	9	14	1	2	3
180—189	9	13	22	4	13	17	2	1	3
190—199	2	6	8	3	5	8		2	2
200—209	1	1	2		2	2		1	1

BlS_{43} (mg./100 ml.)	Non-relatives			Relatives ¹			Children + sibs		
	a	b	c	a	b	c	a	b	c
50—59					1	1			
60—69		1	1						
70—79		1	1						
80—89					1	1			
90—99	1	2	3		5	5		1	1
100—109	4	9	13	3	12	15	3	4	7
110—119	6	13	19	4	13	17	1	4	5
120—129	3	9	12	2	5	7			
130—139	2	8	10	3	8	11		4	4
140—149	6	11	17	2	13	15		3	3
150—159	7	6	13	2	4	6	1	1	2
160—169	5	4	9	3	5	8	1	1	2
170—179	1	2	3	1		1	1		1
180—189		1	1		3	3			

¹ Except for first cousins of diabetics.

Appendix III

Table 1. Correlation coefficients between various somatological factors

Upper rows — Series B. Lower rows — Series A

Bracketed numbers indicate pairs of observation

	Weight	Height	Weight at 13	Height at 13	Birth weight	Birth length	Birth weight of sibs	Mother's weight	Mother's height	Father's weight	Father's height
Fat-free weight	0.67(208)	0.85(208)	0.40(114)	0.43(114)	0.32(161)	0.41(112)	0.31 (97)	0.09(172)	0.40(171)	0.31(159)	0.38(161)
Height	0.58(476) 0.75(107)		0.42(114) 0.53 (40)	0.55(114) 0.76 (40)	0.25(369) 0.25 (76)	0.29(249)	0.30(229) 0.45 (54)	0.15(376) 0.16 (95)	0.38(374) 0.28 (94)	0.23(345) 0.19 (91)	0.39(352) 0.34 (90)
Tibia length	0.52(208) 0.58(104)	0.88(208) 0.78(104)	0.35(114) 0.46 (40)	0.48(114) 0.59 (40)	0.26(161) 0.22 (76)	0.37(112)	0.16 (97) 0.34 (54)	0.13(172) 0.27 (93)	0.39(171) 0.39 (92)	0.27(159) 0.16 (89)	0.40(161) 0.28 (88)
Radius length	0.50(208) 0.57(104)	0.76(208) 0.62(104)	0.33(114) 0.55 (40)	0.37(114) 0.58 (40)	0.20(161) 0.20 (76)	0.24(112)	0.28 (97) 0.22 (54)	0.07(172) 0.22 (93)	0.34(171) 0.33 (92)	0.28(159) 0.09 (89)	0.30(161) 0.19 (88)
Condylar breadth	0.67(208) 0.64(105)	0.60(208) 0.52(104)	0.34(114) 0.49 (40)	0.24(114) 0.47 (40)	0.33(161) 0.28 (76)	0.38(112)	0.32 (97) 0.22 (54)	0.09(172) 0.13 (94)	0.30(171) 0.11 (93)	0.25(159) 0.16 (90)	0.30(161) 0.27 (89)
Bistylloid breadth	0.45(208)	0.40(208)	0.20(114)	0.17(114)	0.24(161)	0.36(112)	0.20 (97)	0.02(172)	0.29(171)	0.17(159)	0.20(161)
Handgrip	0.51(208) 0.57(102)	0.27(208) 0.52(102)	0.25(114) 0.18 (39)	0.11(114) 0.26 (39)	0.22(161) 0.19 (73)	0.18(112)	0.05 (97) 0.29 (53)	0.09(172) 0.03 (94)	0.15(171) 0.03 (93)	0.11(159) 0.00 (90)	0.13(161) 0.10 (89)
Shoulder thrust	0.44(206) 0.46(100)	0.15(206) 0.38(100)	0.23(113) 0.23 (38)	0.10(113) 0.19 (38)	0.16(160) 0.15 (72)	0.10(111)	0.02 (97) 0.02 (52)	0.08(170) 0.03 (89)	0.17(169) 0.03 (88)	0.13(157) 0.00 (85)	0.05(159) 0.03 (84)
Shoulder pull	0.49(206) 0.55(100)	0.20(206) 0.45(100)	0.18(113) 0.18 (38)	0.12(113) 0.31 (38)	0.17(160) 0.17 (71)	0.20(111)	0.06 (97) 0.10 (52)	0.09(170) 0.02 (89)	0.19(169) 0.00 (88)	0.06(157) 0.06 (85)	0.08(159) 0.19 (84)
Skinfold back	0.41(208) 0.40(103)	0.07(208) 0.10(103)	0.32(114) 0.48 (40)	0.08(114) 0.38 (40)	0.09(161) 0.18 (75)	0.03(112)	0.05 (97) 0.12 (53)	0.37(172) 0.11 (92)	0.02(171) 0.16 (91)	0.04(159) 0.12 (88)	0.06(161) 0.17 (87)
Skinfold lat.chest	0.45(208) 0.35(103)	0.09(208) 0.13(103)	0.27(114) 0.55 (40)	0.01(114) 0.44 (40)	0.04(161) 0.08 (75)	0.06(112)	0.16 (97) 0.10 (53)	0.32(172) 0.08 (92)	0.05(171) 0.14 (91)	0.02(159) 0.10 (88)	0.01(161) 0.12 (87)
Skinfold abdomen	0.43(208) 0.46(103)	0.01(208) 0.22(103)	0.23(114) 0.56 (40)	0.02(114) 0.47 (40)	0.01(161) 0.07 (75)	0.06(112)	0.12 (97) 0.02 (53)	0.36(172) 0.17 (92)	0.02(171) 0.00 (91)	0.04(159) 0.13 (88)	0.03(161) 0.21 (87)
Weight minus fat-free weight	0.49(208)	0.24(208)	0.27(114)	0.01(114)	0.02(161)	0.01(112)	0.19 (97)	0.17(172)	0.06(171)	0.01(159)	0.16(161)
Circumf. chest	0.65(146)	0.37(146)	0.33 (87)	0.19 (87)	0.36(111)	0.30 (81)	0.10 (63)	0.18(121)	0.17(120)	0.07(110)	0.02(111)

	Weight at 13	Height at 13	Weight at 13	Height at 13	Birth weight	Birth length	Birth weight of sibs	Mother's weight	Mother's height	Father's weight	Father's height
Size	0.55(114)	0.42(114)	0.43(114)	0.72(114)	0.35 (89)	0.34 (61)	0.23 (54)	0.18 (96)	0.26 (95)	0.17 (90)	0.04 (90)
Weight	0.58 (40)	0.53 (40)	0.52 (40)	0.80 (40)	0.19 (28)	0.35 (89)	0.10 (20)	0.11 (35)	0.01 (35)	0.26 (33)	0.18 (33)
Height	0.36(114)	0.55(114)	0.72(114)		0.32 (89)	0.34 (61)	0.30 (54)	0.14 (96)	0.24 (95)	0.11 (90)	0.02 (90)
at 13	0.65 (40)	0.76 (40)	0.80 (40)		0.16 (28)		0.26 (20)	0.12 (35)	0.20 (35)	0.20 (33)	0.30 (33)
Birth	0.29(369)	0.25(369)	0.35 (89)	0.32 (89)		0.79(249)	0.52(223)	0.13(319)	0.17(318)	0.06(291)	—0.04(298)
weight	0.22 (76)	0.25 (76)	0.19 (28)	0.16 (28)			0.52 (53)	0.16 (74)	0.19 (73)	0.07 (73)	0.02 (72)
Birth											
length	0.33(249)	0.29(249)	0.34 (61)	0.34 (61)	0.79(249)		0.37(124)	0.21(200)	0.24(199)	0.05(186)	0.03(190)
Sibs'											
birth	0.29(229)	0.30(229)	0.23 (54)	0.30 (54)	0.52(223)	0.37(124)		0.15(227)	0.25(227)	0.00(209)	0.03(215)
weight	0.24 (54)	0.45 (54)			0.52 (53)			0.32 (53)	0.21 (52)	0.00 (54)	0.21 (53)
Mother's	0.17(376)	0.15(376)	0.18 (96)	0.14 (96)	0.13(319)	0.21(200)	0.15(227)		0.33(372)	0.07(343)	0.07(348)
weight	0.19 (95)	0.16 (94)	0.11 (35)	0.13 (35)	0.16 (74)		0.32 (53)		0.36 (94)	0.06 (89)	0.16 (88)
Mother's	0.27(374)	0.38(374)	0.26 (95)	0.24 (95)	0.17(318)	0.24(199)	0.25(227)	0.33(372)		0.22(339)	0.22(347)
height	0.08 (93)	0.28 (93)	0.01 (35)	0.20 (35)	0.19 (73)		0.21 (52)	0.36 (94)		—0.04 (88)	0.11 (88)
Father's	0.22(345)	0.23(345)	0.17 (90)	0.11 (90)	—0.06(291)	0.05(186)	0.00(209)	0.07(343)	0.22(339)		0.46(344)
weight	0.20 (90)	0.17 (90)	0.21 (33)	0.20 (33)	0.07 (73)		0.00 (54)	0.06 (89)	—0.04 (38)		0.47 (90)
Father's	0.17(352)	0.39(352)	0.04 (96)	0.02 (90)	—0.04(298)	0.03(190)	0.03(215)	0.07(348)	0.22(347)	0.46(344)	
height	0.36 (89)	0.34 (89)	0.18 (33)	0.30 (33)	0.22 (72)		0.21 (53)	0.16 (88)	0.11 (88)	0.47 (90)	

For evaluation of significance, See Appendix V.

Appendix III

Table 2. Correlation coefficients of intelligence tests.
(Upper rows — Series B. Lower rows — Series A)

		Subtest A	B	C	D	Mean score
	n	465	465	465	465	465 98
Weight	467 109	0.14	0.14	0.11	0.09	0.14 0.02
Height	467 107	0.19	0.17	0.18	0.19	0.22 0.07
Tibia length	208 104	0.04	0.03	0.07	0.00	0.04 —0.00
Radius length	208 104	0.01	0.04	0.04	0.04	0.04 —0.04
Condylar breadth	208 104	—0.00	—0.03	—0.08	—0.02	—0.03 0.03
Bistyloid breadth	208	—0.13	—0.20	—0.20	—0.03	—0.16
Handgrip	208 102	0.04	0.01	0.01	0.16	0.04 0.10
Shoulder thrust	206 100	—0.03	—0.05	0.00	0.13	—0.00 0.00
Shoulder pull	206 100	0.01	0.01	0.08	0.07	0.03 —0.02
Skinfold back	208 103	0.10	0.08	0.09	—0.06	0.06 0.11
Skinfold lat. chest	208 103	0.01	—0.01	0.02	—0.11	—0.03 0.12
Skinfold abdomen	208 103	0.09	0.01	0.03	—0.13	0.00 0.16
Weight at 13	114 40	—0.08	—0.04	0.03	—0.05	—0.01 0.11
Height at 13	114 40	0.02	0.04	0.13	—0.01	0.08 0.05
Birthweight	369 76	0.08	0.10	0.02	0.08	0.08 0.04
Mother's weight	376 95	—0.01	—0.06	—0.01	—0.05	—0.05 —0.13
Mother's height	374 94	0.02	0.04	0.00	0.04	0.04 —0.01
Father's weight	345 91	0.03	0.02	0.02	—0.00	0.01 0.02
Father's height	352 90	0.11	0.07	0.01	0.08	0.08 0.01

Table 2. (Cont).

		Subtest A	B	C	D	Mean score
	n	465	465	465	465	465 98
Manual labour	207 107	—0.30□	—0.31□	—0.27□	—0.10□	—0.29□ —0.32□
Intellectual work	207 107	0.40□	0.43□	0.35□	0.23□	0.42□ 0.48□
School-education	412 108	0.62□	0.59□	0.39□	0.38□	0.60□ 0.56□
Socio-economic level	202 108	0.30□	0.28□	0.16□	0.22□	0.28□ 0.36□
Urbanization	203 106	0.14□	0.18□	0.22□	0.00□	0.15□ 0.09□
Number of						
Father's sibs	374 96	—0.04	—0.03	—0.03	—0.02	—0.04 0.00
Paternal cousins	359 95	0.01	—0.00	—0.06	—0.06	—0.005 0.00
Mother's sibs	384 98	—0.25	—0.24	—0.10	—0.10	—0.20 —0.09
Maternal cousins	365 97	—0.20	—0.18	—0.09	—0.10	—0.17 —0.01
Sibs	398 98	—0.19	—0.17	—0.19	—0.11	—0.20 —0.21
Mother's age at menarche	356 98	—0.13	—0.15	—0.15	—0.15	—0.16 0.05
Mother's age at 1st parturition	374	0.17	0.12	0.12	0.07	0.14

For evaluation of significance, See Appendix V.

Appendix III

Table 3. Length factor correlation coefficients.
(Upper rows Series B — lower rows Series A)

		Height	Tibia	Radius	Shoe size
	n	467 107	208 104	208 104	204 —
Height	467 107		0.88 0.78	0.76 0.62	0.73
Tibia length	208 104	0.88 0.78		0.74 0.68	0.63
Radius length	208 104	0.76 0.62	0.74 0.68		0.64
Shoe size	204 —	0.73	0.63	0.64	
Weight	467 107	0.58 0.74	0.52 0.58	0.50 0.57	0.64
Fat-free weight	208 —	0.85	0.75	0.72	0.76
Condylar breadth	208 104	0.60 0.52	0.51 0.38	0.54 0.40	0.64
Bistyloid breadth	208 —	0.40	0.39	0.43	0.49
Circumf. chest	146 —	0.37	0.36	0.33	0.44
Handgrip	208 102	0.27 0.52	0.23 0.34	0.24 0.41	0.37
Shoulder thrust	206 100	0.15 0.38	0.11 0.16	0.22 0.30	0.26
Shoulder pull	206 100	0.20 0.45	0.17 0.31	0.22 0.37	0.26
Skinfold back	208 103	—0.07 0.10	—0.09 0.10	—0.17 0.07	0.00
Skinfold lat. chest	208 103	—0.09 0.13	—0.09 0.14	—0.14 0.04	0.04
Skinfold abdomen	208 103	0.00 0.22	—0.02 0.22	—0.14 0.12	0.06
Weight minus fat-free weight	208 —	—0.24	—0.21	—0.20	—0.06
Weight at 13	114 40	0.42 0.53	0.35 0.46	0.33 0.55	0.48
Height at 13	114 40	0.55 0.76	0.48 0.59	0.37 0.58	0.34
Birthweight	(161) ¹ 349 76	0.25 0.25	0.26 0.22	0.20 0.19	0.30
Birthlength	(112) ¹ 249 —	0.29	0.37	0.24	0.33

Table 3. (Cont.)

		Height	Tibia	Radius	Shoe size
	n	467 107	208 104	208 104	204 —
Mother's weight	(172) ¹				
	376	0.15	0.13	0.07	0.11
	95	0.16	0.27	0.22	
Mother's height	(171) ¹				
	374	0.38	0.39	0.34	0.35
	94	0.28	0.39	0.33	
Father's weight	(159) ¹				
	345	0.23	0.27	0.28	0.35
	91	0.17	0.16	0.08	
Father's height	(161) ¹				
	352	0.39	0.40	0.30	0.36
	90	0.34	0.28	0.19	
Blood-pressure systolic ²	208	0.22	0.20	0.26	0.23
	104	—0.06	0.00	0.11	
Blood-pressure diastolic ²	208	0.10	0.11	0.13	0.12
	104	—0.21	—0.09	—0.03	
Mean score intel. test	465□	0.22□	0.04□	0.04□	0.05□
	98□	0.07□	0.00□	—0.04□	
School-education	412□	0.20□	—0.02□	—0.02□	0.07□
	108□	0.05□	0.03□	0.09□	

¹ Pair of observations of series B as to tibia, radius and shoe-size.

² Difference between series A and B may be due to an increase of the blood pressure but also to a retardation of growth with longer duration of diabetes.

For evaluation of significance, See Appendix V.

Appendix III

Table 4. Sturdiness factor correlation coefficients.
(Upper rows series B — lower rows series A)

		Condylar breadth	Bistylloid breadth	Circumf. chest
	n	208 104	208 —	146 —
Condylar breadth	208 104		0.61	0.42
Bistylloid breadth	208 —	0.61		0.36
Circumf. chest	146 —	0.42	0.36	
Weight	467 107	0.47 0.57	0.65	0.45
Fat-free weight	208 —	0.82	0.75	0.43
Height	467 107	0.60 0.52	0.40	0.37
Tibia length	208 104	0.51 0.38	0.39	0.36
Radius length	208 104	0.54 0.40	0.43	0.33
Handgrip	208 102	0.41 0.52	0.43	0.48
Shoulder thrust	206 100	0.32 0.39	0.36	0.45
Shoulder pull	206 100	0.31 0.40	0.31	0.51
Skinfold back	208 103	0.13 0.13	—0.12	0.33
Skinfold lat. chest	208 103	0.12 0.21	—0.11	0.31
Skinfold abdomen	208 103	0.14 0.27	—0.10	0.21
Weight minus fat-free weight	208 —	—0.09	—0.24	0.33
Weight at 13	114 40	0.34 0.48	0.20	0.33
Height at 13	114 40	0.24 0.47	0.17	0.19
Birthweight	161 76	0.33 0.28	0.24	0.36
Birthlength	112 —	0.38	0.36	0.30
Mother's weight	172 95	0.09 0.13	—0.02	0.18
Mother's height	171 94	0.30 0.10	0.29	0.17

Table 4. (Cont.)

		Condylar breadth	Bistyloid breadth	Circumf. chest
	n	208 104	208 —	146 —
Father's weight	159 91	0.25 0.16	0.17	0.07
Father's height	161 90	0.30 0.26	0.20	0.02
Blood-pressure systolic	208 104	0.18 —0.04	0.18	0.07
Blood-pressure diastolic	208 104	0.06 —0.08	0.12	0.01
Mean score intel. test	465 98	—0.03□ —0.01□	—0.16□	0.11□
Manual labour	207 107	0.14□ 0.18□	0.36□	0.16□
Intellectual work	207 107	—0.07□ —0.11□	—0.28□	0.02□
School-education	412 108	0.01□ —0.04□	—0.20□	0.00□
Urbanization	203 106	—0.04□ —0.11□	—0.25□	0.08□

For evaluation of significance, See Appendix V.

Appendix III

Table 5. Muscle factors correlation coefficients.
(Upper rows series B — lower rows series A)

		Handgrip	Shoulder thrust	Shoulder pull
	n	208 102	206 100	206 100
Handgrip	208 102		0.73 0.64	0.66 0.58
Shoulder thrust	206 100	0.73 0.64		0.67 0.62
Shoulder pull	206 100	0.66 0.58	0.67 0.62	
Weight	467 107	0.51 0.57	0.44 0.46	0.49 0.55
Fat-free weight	208 —	0.41	0.31	0.31
Height	467 107	0.27 0.52	0.15 0.38	0.20 0.45
Tibia length	208 104	0.23 0.34	0.11 0.16	0.17 0.30
Radius length	208 104	0.34 0.45	0.22 0.31	0.22 0.37
Condylar breadth	208 104	0.41 0.52	0.32 0.39	0.31 0.40
Bistyloid breadth	208 —	0.43	0.36	0.31
Circumf. chest	146 —	0.48	0.45	0.51
Skinfold back	208 103	0.05 0.09	0.05 0.01	0.12 0.15
Skinfold lat. chest	208 103	0.06 0.02	0.06 —0.03	0.12 0.04
Skinfold abdomen	208 103	0.02 0.05	0.00 0.05	0.10 0.04
Weight minus fat-free weight	208 —	0.18	0.21	0.27
Weight at 13	114 40	0.25 0.18	0.23 0.23	0.18 0.18
Height at 13	114 40	0.11 0.26	0.10 0.19	0.17 0.31
Birthweight	160 76	0.22 0.18	0.15 0.14	0.12 0.17
Birthlength	111 —	0.18	0.10	0.20
Mother's weight	170 95	0.09 0.00	0.08 —0.03	0.09 —0.02
Mother's height	169 94	0.15 0.10	0.17 0.00	0.19 0.00

Table 5. (Cont.)

		Handgrip	Shoulder thrust	Shoulder pull
	n	208 102	206 100	206 100
Father's weight	157	0.11	0.13	0.06
	91	0.03	0.03	0.03
Father's height	159	0.13	0.05	0.08
	90	0.05	0.01	0.18
Blood-pressure systolic	208	0.15	0.08	0.10
	104	0.06	—0.15	0.09
Blood-pressure diastolic	208	0.07	0.11	0.05
	104	—0.04	—0.17	—0.02
Manual labour	207□	0.29□	0.30□	0.19□
	107□	0.29□	0.28□	0.27□
Intellectual work	207□	0.11□	—0.19□	—0.10□
	107□	0.03□	0.11□	0.14□
School-education	412□	—0.07□	—0.08□	—0.03□
	108□	—0.11□	—0.15□	—0.06□
Urbanization	203□	—0.07□	—0.08□	—0.03□
	106□	—0.17□	—0.15□	—0.03□

For evaluation of significance, See Appendix V.

Appendix III

Table 6. Fat factor correlation coefficients.
(Upper rows Series B — lower rows Series A)

		Skinfold back	Skinfold lat. chest	Skinfold abdomen	Weight minus fat-free weight
	n	208 103	208 103	208 103	208 —
Skinfold back	208 103		0.86 0.71	0.84 0.73	0.60
Skinfold lat. chest	208 103	0.86 0.71		0.84 0.85	0.66
Skinfold abdomen	208 103	0.84 0.73	0.84 0.85		0.57
Weight minus fat-free weight	208 —	0.60	0.66	0.57	
Weight	467 107	0.41 0.40	0.45 0.35	0.43 0.46	0.49
Fat-free weight	208 —	—0.05	—0.05	—0.00	—0.28
Height	467 107	—0.07 0.10	—0.09 0.13	0.00 0.22	—0.24
Tibia length	208 104	—0.09 0.10	—0.09 0.14	—0.02 0.22	—0.21
Radius length	208 104	—0.17 0.07	—0.14 0.04	—0.14 0.12	—0.20
Condylar breadth	208 104	0.13 0.13	0.12 0.21	0.14 0.27	—0.09
Bistyloid breadth	208 —	—0.12	—0.11	—0.10	—0.29
Circumf. chest	146 —	0.33	0.31	0.21	0.33
Handgrip	208 102	0.05 0.08	0.06 —0.02	0.02 0.04	0.18
Shoulder thrust	206 100	0.05 0.01	0.06 —0.02	0.00 —0.05	0.21
Shoulder pull	206 100	0.12 0.15	0.12 0.04	0.10 0.04	0.27
Weight at 13	114 40	0.32 0.48	0.27 0.55	0.23 0.56	0.27
Height at 13	114 40	0.08 0.38	—0.01 0.44	0.02 0.47	—0.02
Birthweight	161 76	0.09 —0.18	0.04 —0.08	0.03 —0.07	0.02
Birthlength	112 —	0.03	0.06	—0.06	—0.01
Mother's weight	172 95	0.37 0.11	0.32 0.08	0.36 0.16	0.17

Table 6 (Cont.)

		Skinfold back	Skinfold lat. chest	Skinfold abd.	Weight minus fat-free weight
	n	208 103	208 103	208 103	208 —
Mother's height	171	—0.02	—0.05	0.02	—0.06
	94	—0.16	—0.14	0.00	
Father's weight	159	—0.04	0.02	0.04	0.01
	91	0.12	0.10	0.13	
Father's height	161	—0.06	—0.02	0.03	—0.16
	90	0.17	0.12	0.21	
Blood-pressure systolic	208	0.05	0.04	0.04	0.06
	104	0.27	0.16	0.15	
Blood-pressure diastolic	208	0.05	0.07	0.02	0.08
	104	0.16	0.05	0.03	
Hairgrowth chest ¹	208	0.23□	0.21□	0.17□	0.22□
	103	0.24□	0.14□	0.20□	
Manual labour	207	—0.17□	—0.12□	—0.20□	—0.03□
	107	0.00□	—0.16□	—0.07□	
Intellectual work	207	0.15□	0.09□	0.18□	0.09□
	107	0.15□	0.11□	0.10□	
School-education	412	0.12□	0.04□	0.14□	0.05□
	108	—0.02□	0.15□	0.06□	
Urbanization	203	0.22□	0.16□	0.16□	0.11□
	106	—0.21□	0.03□	0.00□	

¹ Judged by a five-grade continuous scale according to LINDEGÅRD (1956).

For evaluation of significance, See Appendix V.

Appendix III

Table 7. Coefficients of correlation between blood pressure and various somatic data.
(Upper rows series B — lower rows series A)

		Syst.	Diast
	n	208 104	208 104
Systolic pressure	208 104		0.60 0.69
Diastolic pressure	208 104	0.60 0.69	
Weight	467 107	0.21 0.19	0.11 0.02
Fat-free weight	208	0.27	0.14
Height	467 107	0.22 —0.05	0.10 —0.21
Tibia length	208 104	0.20 0.00	0.11 —0.09
Radius length	208 104	0.26 0.11	0.13 —0.03
Condylar breadth	208 104	0.18 —0.04	0.06 —0.08
Bistylloidbreadth	208	0.18	0.12
Circumf. chest	146	0.07	0.01
Handgrip	208 102	0.15 0.06	0.07 —0.04
Shoulder thrust	207 100	0.08 —0.15	0.11 —0.17
Shoulder pull	206 100	0.10 —0.11	0.05 —0.09
Skinfold back	208 103	—0.02 0.27	—0.02 0.16
Skinfold lat. chest	208 103	0.00 0.16	—0.01 0.05
Skinfold abdomen	208 103	0.06 0.15	0.02 0.03
Weight minus fat-free weight	208	—0.03 0.46	—0.03 0.24

Appendix IV.

Table 1. In the calculation of the risk of a person with a diabetic relative being a diabetes gene carrier with the possibility of developing diabetes the following expressions were used (largely according to HULTKRANTZ & DAHLBERG, 1927).

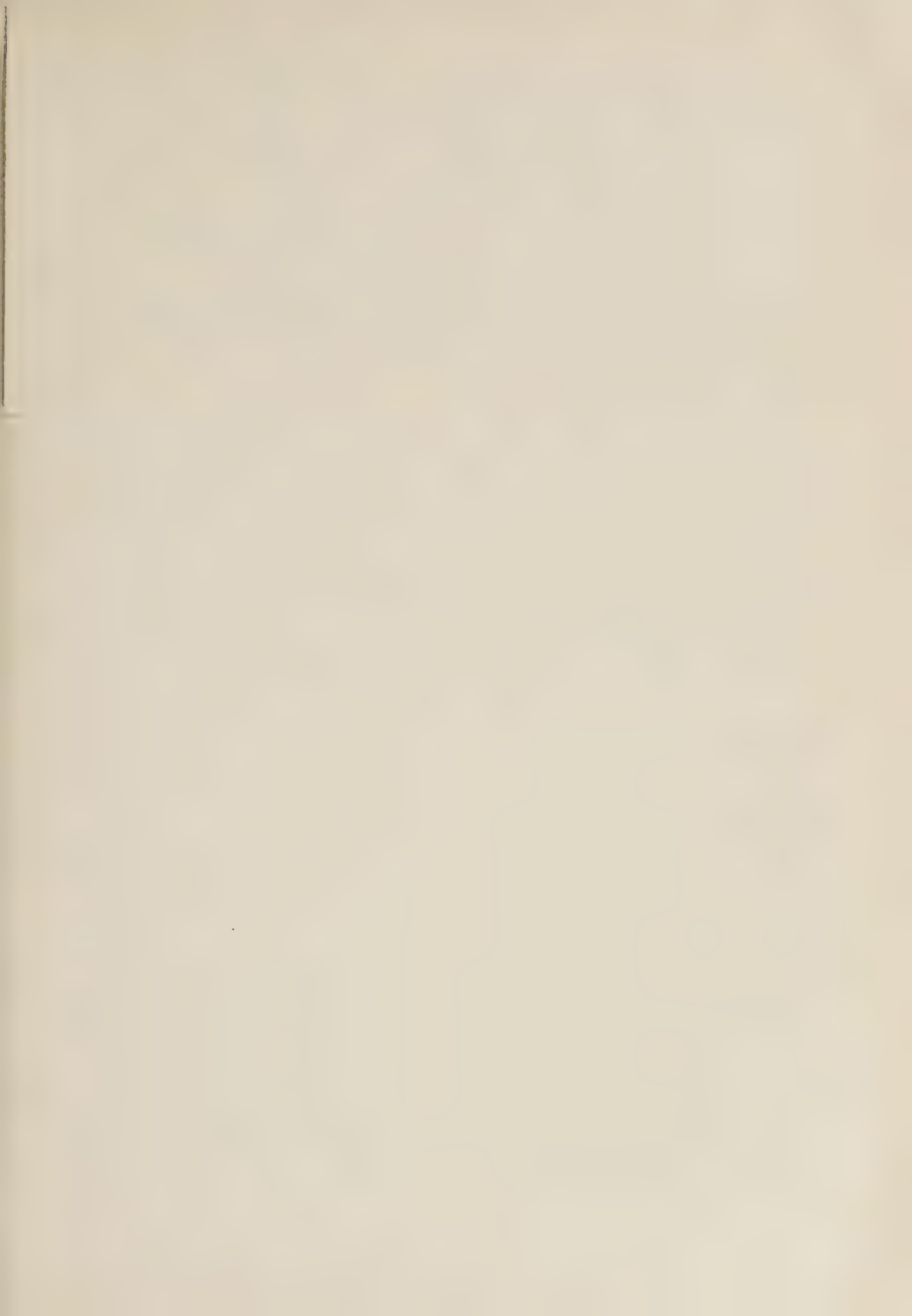
The proportion of the assumed diabetes inducing gene in the population is p and of corresponding normal allele q , where $p + q = 1$.

Diabetic relative \ Inheritance	Recessive	Dominant
Sib	$1/4 (1+p)^2$	$1 - \frac{q^2(3+q)}{4(1+q)}$
Parent or child	p	$1 - \frac{q^2}{1+q}$
Grandparent, uncle or aunt	$1/2 p (1+p)$	$1 - \frac{q^2(2+q)}{2(1+q)}$
First cousin	$1/4 p (1+3p)$	$1 - \frac{q^2(4+3q)}{4(1+q)}$

Appendix IV

Table 2. Risk of being a gene carrier able to develop a disease on assuming different frequencies of a mutant, pathogenic allele, and recessive or dominant inheritance.

Gene-frequency		Recessive inheritance								Dominant inheritance							
Type of relative		1/2	1/4	1/5	1/6	1/7	1/8	1/∞		1/2	1/5	1/10	1/100	1/∞			
Sib		0.56	0.39	0.36	0.34	0.33	0.32	0.25		0.85	0.66	0.59	0.51	0.50			
Parent or child		0.50	0.25	0.20	0.17	0.14	0.13	0		0.83	0.64	0.57	0.51	0.50			
Grandparent, uncle or aunt		0.38	0.16	0.12	0.10	0.08	0.07	0		0.79	0.50	0.38	0.26	0.25			
First cousin		0.31	0.11	0.08	0.06	0.05	0.04	0		0.77	0.43	0.29	0.14	0.13			
No relative		0.25	0.06	0.04	0.03	0.02	0.02	0		0.75	0.36	0.19	0.02	0			



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